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SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT

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CONTENTS

FINDINGS AND CONCLUSIONS

The Federal role in the health sphere has increased dramatically in the past three decades. One of the primary areas of concentration in this growing involvement has been the encouragement of new knowledge through the support of biomedical research. Many observers wholeheartedly agree that support for research is essential to improving the health of the American people.

By fiscal year 1974, combined public and private sector support for health research and development totalled an estimated $4.3 billion, with $2.8 billion, 65% of the total, coming from the Federal government. During that year, 62% of the Federal research expenditure was administered by the National Institutes of Health (NIH).

NIH is recognized nationally and internationally as a focus of excellence in biomedical research. Yet the past seven years have seen increasing questioning of the role and functioning of the institution, both from inside and outside NIH. The biomedical research community has been concerned about the adequacy of levels of funding for research and about political interference in the administration of NIH. The Administration, the Congress, and the public have, in various ways, raised questions about the proper role of NIH in assuring a healthy population. Some have feared for the survival of the institution itself. Despite the questioning, and at times even serious controversy, NIH remains a high-quality research establishment which carries out its activities in a highly professional and responsible way—however, not without fault nor opportunities for improvement. Because NIH is so important and such an excellent institution, the challenge now is to preserve and strengthen it. This report seeks to analyze and offer specific recommendations for meeting this challenge.

NIH is a complex institution, made up of eleven research institutes, several support divisions, and the National Library of Medicine. Ten institutes conduct intramural research programs within the walls of NIH; these programs consume about 10% of the NIH appropriation. Most of the remainder of NIH activities are carried out through grants and contracts to universities, nonprofit research institutes, and commercial firms. Grants support research, research training, construction, and other activities. Contracts generally support "targeted" research, that is, research done with a specific goal in mind. During fiscal year 1974, $765 million was distributed as regular grants, $335 million as research and development contracts, and $246 million as centers, resources, and other grants. These mechanisms have in general worked well administratively, and have helped to change the nature of modern medicine and the disease patterns in the U.S. population.

Chronic diseases such as diseases of the heart, cancer, and stroke now cause the great majority of deaths. These diseases seem to be considerably more complicated than the previously significant infectious diseases, and behavioral and environmental factors appear

to be implicated in the causation of these chronic diseases. For example, it is estimated that environmental factors cause 70 to 90% of cancers. Yet it is far from clear that research priorities at NIH have changed in response to the changing challenge. *It is therefore recommended that research priorities at the National Institutes of Health be critically reconsidered. The complicated etiology of chronic diseases seems to warrant expanded support for environmental and behavioral research to assure that the biomedical research community, both within and outside of NIH, is attentive to the evidence as to the environmental and behavioral etiology of the most significant chronic diseases.* (See Chapter 1, pages 4–6.)

Behavioral research findings indicate that personal lifestyle is very important in producing disease. Such factors as cigarette smoking, lack of exercise, and diet are clearly critical to health. At present, there is insufficient information to indicate how to most effectively change personal habits. Therefore, *it is recommended that more research be devoted to methods of education of the public to change health behavior.* (See Chapter 1, pages 4–6)

A particular problem of research resources in almost all the important disease areas is the shortage of epidemiologists. Epidemiology has produced most of the research findings indicating the cause of chronic disease. Therefore, *it is recommended that NIH give serious attention to the problem of lack of epidemiological resources, with a view to taking vigorous action to foster epidemiological resources and epidemiological research. This will require development through the programs of the various institutes, and may also require increased funding for other health agencies as well, notably the National Center for Health Statistics.* (See Chapter 1, page 6 and Chapter 8, page 68)

The mission of NIH has classically been to increase medical knowledge and to develop ways in which providers of medical care can intervene safely and effectively to prevent, treat, or cure diseases and disabilities. NIH has pursued this mission through the support of biomedical research and development, research training, development of research resources, and the communication of the findings of the research. However, NIH alone does not determine its missions and it has come under increasing pressure to expand or organizationally subdivide its responsibilities. In some cases, activities have been mandated by the Congress or the Administration to expand its mission. In particular, four new functions have been stressed:

(1) Evaluation of the application of research findings, especially through controlled clinical trials and through short-term demonstration and control programs in local communities.

(2) Application of research findings through coordination with other Federal agencies, dissemination of information to providers, and education of the public.

(3) Cooperation with government-wide efforts to resolve special national health problems.

(4) Provision of scientific consultation in the development of new programs to improve the nation's health.

Of these functions, the first 1 has received the most widespread attention. Demonstration and control is a rapidly growing activity at NIH, yet not all institutes support such programs; this may be a problem in need of policy resolution. The largest such effort is in the National Cancer Institute, particularly in the Comprehensive Cancer

centers program and in Cancer Control. *The Comprehensive Cancer Centers Program suffers from a lack of clear goals and philosphy and regional coordination; and it is recommended that these problems be actively addressed.* (See Chapter 4, pages 22–24).

In the area of evaluation, a dual problem is apparent. Some research findings of potential value have not been disseminated as rapidly or as effectively as they should have been, and there have been lengthy delays in some cases. On the other hand, procedures and technologies are in some cases accepted throughout the medical care system too quickly, without adequate scientific validation of their efficacy. The former problem has received a great deal of attention; the latter has been largely ignored. The primary method of assessment is the controlled clinical trial. Although controlled clinical trials already make up more than 5% of the NIH activity, the information from these trials is not always used wisely. For example, a procedure or technology found to be ineffective or marginally effective may be paid for under government financing programs. Therefore, *it is recommended that more attention be given to the effective dissemination and use of information from these trials, especially through inter-governmental coordination. It is further recommended that the question of funding of controlled clinical trials be examined critically by the Department of HEW, with the hope of developing alternative funding sources beyond NIH, particularly with regard to the evaluation of current approaches and technologies applied in medical practice, possibly as a percentage tap on Medicare funds.* (See Chapter 4, pages 25–27).

The purpose of the intramural program at NIH has been increasingly questioned in recent years. However, this program continues to be a high-quality research activity, and the basic justifications for an internal capacity for research remains intact. This function deserves continuing support. However, there are administrative problems in the intramural program which need to be addressed. Mechanisms for critical peer review of research work appear to be undeveloped. A particular problem which is becoming increasingly apparent is that of the aging civil service career scientist who loses productivity, but encumbers valuable space and research resources. *It is therefore recommended that NIH management be directed to implement and monitor a program wherein the program and the productivity of each laboratory or branch would be carefully and critically reviewed periodically. It is further recommended that the NIH leadership address itself to the problem of the unproductive scientist.* (See Chapter 5, pages 33, 34).

A related problem is that of allocation of resources. The allocation of hospital beds in the Clinical Center to the various institutes has not been sufficiently re-evaluated and adjusted with regard to research priorities. Furthermore, the mechanisms for changing the allocation of related resources such as space, equipment, and so forth, have proven to be less than satisfactory. *It is therefore strongly recommended that the allocation of beds in the Clinical Center be critically evaluated and appropriate reallocation be made as rapidly as possible. It is further recommended that the allocation of resources in the entire intramural program be similarly evaluated periodically.* (See Chapter 5, pages 36, 37).

The process for peer review of grant applications needs to be strengthened. As previously noted, most of the biomedical research funded by NIH takes place at other institutions. The usual mechanism is the research grant. Grant applications are reviewed by 53

regular study sections of outside scientists organized on the basis of a categorization of the specialties in the field of science. Each grant is then assigned, as appropriate, to one of the institutes, where it is reviewed by the national advisory council for that institute. The study section reviews the application solely on the basis of its scientific merit and gives it a priority score. The national advisory council, which includes lay membership, and which have, by statute, the final authority for approval or disapproval, is expected to serve a broader function, assessing relevance, value to society, and so forth.

Many observers of NIH feel that the study sections, often referred to as "the peer review system," are the essential backbone of the organization. However, there have been concerns expressed about this mechanism including possible conflicts of interest, the institutional and geographic spread of members, and the infrequent appointment of younger scientists to study sections. While it seems that the issue of institutional and geographic spread has been adequately dealt with, *it is recommended that the issues of possible conflicts of interest and appointment of young scientists (under the age of 36) be formally addressed by NIH management.* (See Chapter 6, pages 43, 44).

The broadly constituted advisory councils are not used effectively in helping to set priorities and develop policies for most institutes. One significant impediment is partisan political clearance problems and related long delays in filling empty slots. The recently escalated and undue meddling should be stopped. If the political interference can be ameliorated, *greater attention to selection of a more representative variety of disciplines and greater emphasis on subject matter orientation are two recommended ways to improve advisory council functioning.* (See Chapter 6, pages 45–49).

Once a grant is awarded, NIH considers that it has a "moral obligation" to continue funding until the term of the grant, usually three years, has ended. Yet it may sometimes be possible to determine before the end of that time that the quality of performance or the extent of research progress is unacceptable. In the situation of a high degree of competition for support, such monies might be spent more fruitfully on other projects. Interim and final reports are not carefully reviewed, and are sometimes not even received. *It is recommended that performance evaluation and accountability mechanisms for grants be strengthened.* (See Chapter 6, pages 50, 51).

In terms of contracts, the research community generally feels that these are less effective than grants and should be de-emphasized. However, there are clear justifications for and advantages to contract work for some types of activity; it should not be a question of either-or. Internal review of request for proposals (RFPs) is important to assure good proposals for contracts. Peer review has been used increasingly to strengthen the contract process, and *it is recommended that it be extended such that all research contract proposals be reviewed and be subject to approval by the national advisory council, or a special subcommittee thereof, of the appropriate institute before issuance of RFPs.* (See Chapter 6, page 58).

A final problem in the extramural program is that of overhead payments to grantee institutions for general institutional support. In recent years, the capability of the Department of HEW to negotiate fair overhead rates has deteriorated. *It is therefore recommended that the*

Department make a special effort to upgrade its capability to assess and successfully negotiate fair overhead rates. (See Chapter 6, pages 51, 52).

The organization of NIH also has some problems, although it has in general worked well:

(1) Each institute functions rather autonomously, and some have developed extremely interesting and unique methods of carrying out their individual missions. *It is therefore recommended that a mechanism of comparative evaluation and communication be developed by NIH management.* (See Chapter 8, pages 63, 64, 66, 67).

(2) The Director of NIH is, in effect, the leader of biomedical science, but lacks the resources necessary to do his job. In particular, *it is recommended that the Director develop and seriously implement improved management accountability mechanisms which will periodically assess each area of science and the performance of each institute in its related research programs.* (See Chapter 8, page 64).

(3) Many problems of coordination and communication with other parts of the Federal government are apparent. NIH has a great potential capacity to contribute its skills and knowledge but has been less than fully willing to commit itself. *It is recommended that NIH devote much more attention to this problem.* (See Chapter 8, pages 66–68).

Finally, NIH suffers from serious practical administrative problems. During the period 1968 to 1976, NIH programs increased by $768 million, while personnel has declined by 540 positions due to personnel ceilings. This problem has become particularly acute since 1971. Another practical problem concerns space, with NIH personnel scattered in numerous locations. *It is therefore recommended that the Department of HEW and the Office of Management and Budget examine Congressionally-mandated activities to assure that they are adequately housed and staffed and NIH's management mechanisms for critically evaluating the effectiveness of using existing staff in light of changing priorities and individual program performance.* (See Chapter 9, pages 71–73, 75, 76).

INTRODUCTION

This investigation of the National Institutes of Health (NIH) was undertaken at the request of and under the direction of Congressman Paul G. Rogers, Chairman of the Subcommittee on Health and the Environment, House Interstate and Foreign Commerce Committee. The investigation was stimulated by the difficulties which the Federal biomedical research effort has experienced since the retirement of Dr. James Shannon as Director of NIH in 1968. Active attempts have been made to prevent Congressional access to the undirected professional advice of career professionals within NIH. A series of proposals have been made by the Administration, several of which have been quite disturbing to the biomedical research community.

Dr. Shannon has recently summarized some of these proposals.[1] "The proposal to abandon or radically modify the NIH peer review system for research grants. This proposal seems to have been abandoned, at least temporarily. (2) The institution of third party payment for patient services provided to research subjects within the NIH Clinical Center. This proposal also seems to have been abandoned. (3) The proposal to abandon the Fellowship and 'training' programs of NIH. Termination of Federal support for graduate education continues to be a goal except perhaps in the case of National Cancer Institute programs. Substitute programs are limited to a modest post-doctoral fellowship program in narrowly selected shortage areas and to general loan programs." There are also some proposals still under consideration: "(1) The abolishment of the categorical structure of NIH; the use of Federal support dollars to exert direct pressure on medical schools to modify their perceptions of their educational mission."

Dr. Shannon also summarizes the factors of particular concern to the biomedical research community: (1) the intent to abandon Federal support for graduate education, (2) an emphasis in program development on short term social need rather than a balanced consideration of this and scientific opportunity, (3) the emphasis on the central direction of research, and (4) the absence of generally agreed upon policy guides that can secure some constancy of objectives as the base for program development.

These changing proposals and the feeling of uncertainty in the biomedical research community stimulated Chairman Rogers to undertake a Congressional Study of NIH. There has not been a recent Congressional investigation of the NIH, although the report of the President's Biomedical Research Panel, which is due in 1976, is a Congressionally mandated activity.

The investigation was undertaken not to refute the policy alternatives discussed above, but to try to strengthen the institution. It was

[1] Shannon, James A., "Federal and Academic Relationships The Biomedical Science of 1974," From Proceeding of the National Academy of Science, Vol. 71, pages 3309–3316, August, 1974.

clearly recognized that NIH must change, and that some of the proposals set forth by Dr. Shannon may very well be constructive and necessary.

In carrying out the study, previous investigations were reviewed, especially those chaired by Woolrigde [2] and Ruina.[3] In addition previous Congressional investigations were reviewed, including one chaired by Mr. Rogers [4] and a series of reports by the Inter-Governmental Relations Subcommittee of the House Government Operations Committee, Lawrence H. Fountain, Chairman.[5 6 7]

During the investigation, more than 100 individuals were interviewed in depth, including past leaders of NIH, outside scientists, journalists, and many staff persons presently at NIH, including the Director and all institute directors. These off-the-record interviews were then followed up in whatever fashion seemed appropriate. A great number of internal NIH reports were reviewed, and much new information was also collected and analyzed.

Those at NIH were consistently cooperative and helpful, and deserve great credit for the assistance given. The Office of the Assistant Secretary of Health and the Office of the Assistant Secretary for Planning and Evaluation also cooperated effectively.

Because of time limitations, the National Institute of Mental Health was not investigated. The intramural research program of that Institute remains on the NIH campus, although the entire Institute was removed from NIH in 1968, and became part of the Alcohol, Drug Abuse and Mental Health Administration in the reorganization of 1973. The study focused on the intramural and extramural programs of NIH, as well as the organization of the institution. Training programs were also examined, but only superficially, as this area is very much in a state of change.

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[2] "Biomedical Science and Its Administration: A Study of the National Institutes of Health," Report to the President by the NIH Study Committee, Dr. Dean F. Woldridge, Chairman, U.S. Government Printing Office, Washington, D.C., 1965.

[3] "Report of the Secretary's Advisory Committee on the Management of National Institutes of Health Research Contracts and Grants," Jack P. Ruina, Chairman, D.H.E.W., U.S. Government Printing Office, March, 1966.

[4] Investigation of the Department of Health, Education, and Welfare, Report of the Special Subcommittee, U.S. Congress, House of Representatives, Committee on Interstate and Foreign Commerce, 89th Congress, Second Session, pages 107–132.

[5] "Health Research and Training, The Administration of Grants and Awards by the National Institutes of Health," Second Report by the Committee on Government Operations, House of Representatives, 87th Congress, 1st Session, April 28, 1961.

[6] "Administration of Grants by the National Institutes of Health," Twenty-First Report by the Committee on Government Operations, House of Representatives, 87th Congress, June 30, 1962.

[7] "The Administration of Research Grants in the Public Health Service," Ninth Report by the Committee on Government Operations, House of Representatives, 90th Congress, 1st Session, October 20, 1967.

INVESTIGATION OF THE NATIONAL INSTITUTES OF HEALTH

CHAPTER 1

The Value of Health Research

The importance of a healthy population is self-evident. The Federal government has undertaken various tasks in the health sphere in an attempt to assure such a population. One of the clearest Federal responsibilities in health has been to support biomedical research for the purpose of increasing basic knowledge. This effort has been supported with large amounts of Federal tax dollars because the benefits of broadly-based basic research activities accrue to all of soceity and not just to specific individuals or groups.

Health research has been defined by the National Institutes of Health (NIH) as follows: "Health-related research involves systematic study directed toward the development and use of scientific knowledge in the following areas: (1) The causes, diagnosis, treatment, control, prevention of and rehabilitation relating to, the physical and mental diseases and other killing and crippling impairments of mankind; (2) The origin, nature and solution of health problems not identifiable in terms of disease entities; (3) Broad fields of science important to or underlying disease and health problems; and (4) Research in nutritional problems impairing, contributing to, or otherwise affecting optimum health."

The achievements of the biological sciences in the past few decades have been truly remarkable. An interesting publication sponsored by the American Biology Council summarizes these achievements.[1] On the other hand, progress of medicine during those same decades has been less certain. The health of the population as measured by life expectancy or mortality rates has not changed as dramatically as one might expect, observing the extent of the achievements in the biomedical sciences. For example, as shown in Table 1, the life expectancy of 65 year olds increased only about 3 years between 1900 and 1971. Life expectancy of white males at age 65 increased even less, only about one year. Formidable diseases such as cancer, heart disease and arthritis are still unsolved and lacking satisfactory treatment.

This has led to pressures for more targeted research to achieve health goals. Dr. Lewis Thomas [2] has made the following remarks about this tendency: "One trouble with this view is that it attributes to biology and medicine a much greater store of usable information with coherence and connectedness than actually exists. In real life the biomedical sciences have not yet reached the stage of any kind of

[1] American Biology Council, "Contribution of the Biological Sciences to Human Welfare," Federation Proceedings, November-December, 1972, Part 2.

[2] Thomas, Lewis, "The Planning of Science," *The Lives of a Cell*, New York, The Viking Press, 1974, pages 115-120.

general applicability to disease mechanisms. In some respects we are like the physical sciences of the early twentieth century, booming along into new territory but without an equivalent for the engineering of that time. It is possible that we are on the verge of developing a proper applied science, but it has to be said that we don't have one yet. The important question before the policy makers is whether this should be allowed to occur naturally as a matter of course, or whether it can be ordered up more quickly under the influence of management and money." The practically unanimous opinion of the scientific community is that it cannot; however, among the public and an increasingly large group in Congress, the opinion is not so unanimous.

TABLE 1.—AVERAGE REMAINING LIFETIME IN YEARS AT SPECIFIED AGES, UNITED STATES, 1900 AND 1971, AND PERCENTAGE CHANGE BETWEEN 1900 AND 1971

Age in years	Life expectancy		Years difference	Percent change
	1900	1971		
0	49.2	71.0	21.8	44.3
5	55.0	67.6	12.6	22.9
15	46.8	57.9	11.1	23.7
25	39.1	48.8	9.5	24.3
35	31.9	39.3	7.4	23.2
45	24.8	30.3	5.5	22.2
55	17.9	22.1	4.2	23.5
65	11.9	15.1	3.2	26.9
75	7.1	[1] 9.1	[1] 2.0	[1] 28.2
85	4.0	[1] 4.8	[1] .8	[1] 20.0

[1] Figures for 1968.

Source: Data derived from Statistical Abstract of the United States, 1971, Bureau of the Census, U.S. Department of Commerce, 1971, and Statistical Abstract, 1974.

The Value of Basic Research

Most biomedical researchers are convinced that basic undirected research is essential to the prevention, diagnosis and treatment of disease, and they can support their convictions with dramatic examples. Comroe and Dripps [3] have cited the following examples:

1. When Roentgen discovered x-rays, it was not to enable a cardiologist to visualize the coronary arteries of a patient suffering from angina pectoris; he was studying a basic problem in physics to determine the electrical nature of matter.
2. When Carl Landsteiner discovered blood groups it was not part of a program to make blood transfusions safe; he was investigating basic problems in immunology.
3. When Cournand and Richards passed a catheter into the heart of man, it was not to develop a new method of diagnosing heart disease; they were attempting to measure the oxygen content of mixed venous blood in the right atrium of the heart.
4. When Shackell developed a technique of freeze drying in 1909, it was not to preserve penicillin without loss of potency or to preserve plasma or its fractions; he was studying a basic problem of the water content of liver and muscle.
5. When Clarke, collector and amateur breeder of butterflies, studied variations in the color of butterfly wings, he had no idea

[3] Comroe, J. D. and Dripps, R. D., "Ben Franklin and Open Heart Surgery," *Circ. Res.* 35: 661–669, Nov. 1974.

that it would lead to the discovery of the Rh factor in human blood.

6. When Davies and Brink devised an electrode for measuring the partial pressure of oxygen, it was not to monitor blood-oxygen in the intensive care unit; they were carrying out basic research.

A problem that the basic research community has is convincing the outside world that basic research is indeed worthwhile. This can only be done retrospectively. Comroe and Dripps in the previously cited article trace the fundamental knowledge necessary for the full development of open-heart surgery. Open-heart surgery was selected because a poll of physicians and surgeons chose that as the most important clinical advance in cardiovascular and pulmonary medicine and surgery since 1945. Twenty-five fundamental bodies of knowledge were identified which were essential for the full development of open heart surgery.

The National Science Foundation [4] has prepared a similar assessment of selected critical events in science, including the case of the oral contraceptive. The tracing begins in 1849 with the discovery of the male sex hormones, and involves more than thirty basic science discoveries.

Fudenberg [5] attempted to assess some cost benefits of basic research, primarily by using poliomyelitis as an example. In the six year period from 1955 to 1961, monetary savings resulting from the prevention of polio cases are estimated to be more than $6 billion, or about $1 billion per year. Current savings are estimated to be about $2 billion per year, about the current NIH appropriation. Thus, polio alone could be said to have justified the investment in basic research.

Fudenberg [6] also estimated savings in other diseases. He estimated that tuberculosis chemotherapy resulted in a saving of about $5 billion in the period 1954 to 1969. He estimated measles vaccine to have saved $423 million from 1963 to 1968. Carr [7] estimated savings of $110 million over a period of time by eradication of hemolytic disease. And Diamond [8] pointed out the great savings which will occur in the future as the result of the anticipated disappearance of erythroblastosis fetalis (resulting from Rh incompatibility between mother and fetus). These few examples show the potential to be gained from research which can be applied to prevent disease.

An official of NIH estimated recently that about 27% of the NIH budget presently goes to support basic research.[9] Some feel that basic research has less overall support now than previously, but evidence for the assertion is lacking. The Director of the National Cancer Institute asserted that basic research support has risen in his Institute.

APPLIED SCIENCE

Thomas describes applied science as follows: "When you are organized to apply knowledge, set up targets, produce a usable product, you require a high degree of certainty from the outset. All the facts

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[4] The Illinois Institute of Technology Research Institute, *Technology in Retrospect and Critical Events in Science*, The National Science Foundation, December 15, 1968.

[5] Fudenberg, H. H., "Fiscal Returns of Biomedical Research," *J. Invest. Dermatol.* 61: 321-329, 1973.

[6] Fudenberg, H. D., "Economic Savings Derived from Biomedical Research," Mimeograph, Undated.

[7] Carr, M. C., "Economic Savings for Eradication of Hemolytic Disease," Mimeograph, 1971.

[8] Diamond, L. K., "Statistics Regarding Erythroblastosis and Rh Sensitization in Women," Mimeograph, 1970.

[9] Fredrickson, Donald, Testimony Before the President's Biomedical Research Panel, November 24, 1975.

on which you base protocols must be reasonably hard facts with unambiguous meaning. The challenge is to plan to work and organize the workers so that it will come out precisely as predicted. For this you need centralized authority, elaborately detailed time schedules, and some sort of reward system based on speed and perfection. But most of all you need the intelligible basic facts to begin with, and these must come from basic research. There is no other source."

One problem is that there *are* lags in application. Comroe and Dripps cite some of the most striking of these. Closed chest cardiac massage has been used in physiology laboratories since 1878 to resuscitate cats and dogs but was not applied to man until 1960. Vesalius demonstrated artificial ventilation in 1543. Physiologists used it in laboratory experiments in the 1800's but it was not used on a patient until 1915. Alexis Carrel performed virtually every feat and developed every technique know to vascular surgery today between 1902 and 1910, but his work was essentially lost until 1940. Long lags also occured in the use of heparin, hemodialysis, the cathode ray oscilloscope, telemetry and techniques of vascular surgery. These are only application lags in the area of cardio-pulmonary medicine and surgery. The list could be lengthened using other parts of medicine. A recent example is echocardiography, which has been known experimentally since the 1940's, but is only now coming into application.[10] If developed earlier, much invasive cardiac catheterization could possibly have been avoided during the 1950's and 1960's. For this reason it seems appropriate that there be an area of directed or targeted research and development.

NEED FOR A NEW PARADIGM

The patterns of disease in this country have undergone a marked change in the last decades. Figure 1 shows causes of death for the United States in 1900 and 1967. Chronic diseases such as diseases of the heart, cancer and stroke now cause the great majority of deaths, whereas in 1900 the majority of deaths were caused by infectious diseases. The control of infectious diseases has been possible because a microorganism such as a bacteria or virus has been identified as a necessary cause of each. Effective prevention or treatment has then been possible in each case.

All the evidence indicates, however, that the chronic diseases are considerably more complicated. In particular, factors such as diet, air quality, and stress have been implicated. This seems to indicate the need for some change in emphasis in biomedical research. This area is already gaining increasing interest in the National Cancer Institute. A recent staff paper at the Interagency Collaborative Group on Environmental Carcinogenesis summarized the evidence that environmental factors cause 70 to 90% of cancers.[11] A report of a Subcommittee of the National Cancer Advisory Board recently estimated that only 10% of the Institute's budget is invested in environmental research, and recommended an increase.[12]

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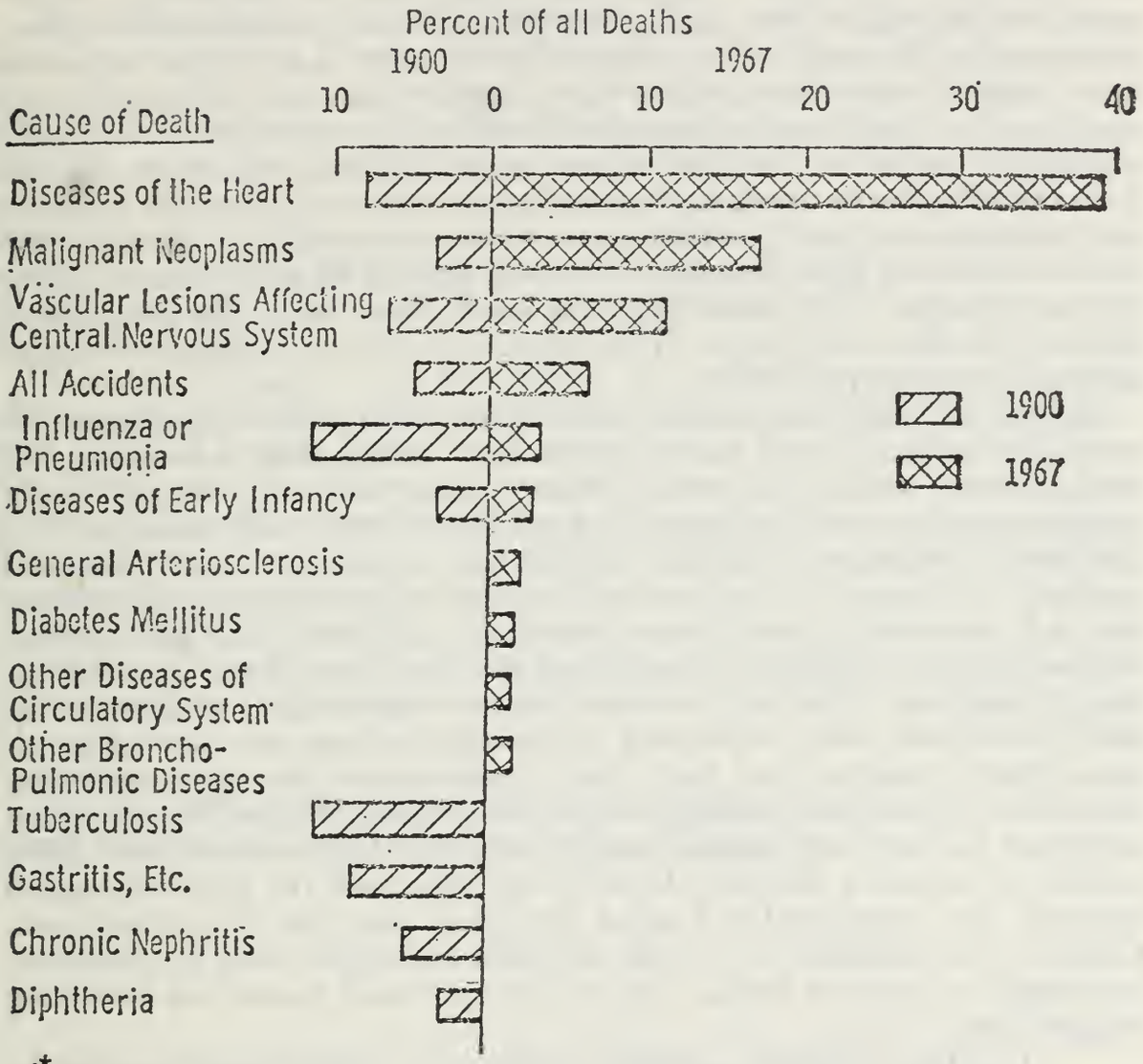
[10] Feigenbaum, H., *Echocardiography*, Philadelphia, Lean & Febiger, 1973.

[11] Schneiderman, M. A., "Cancer—A Social Disease?" Presented at the Interagency Collaborative Group on Environmental Carcinogenesis, June 11, 1975.

[12] Report of the Subcommittee on Environmental Carcinogenesis, Presented at the March 17-18, 1975 meeting of the National Cancer Advisory Board.

Percent of All Deaths, by Specified Causes of Death* (U.S.A., 1900** and 1967).



*10 leading causes of death in 1900 and 1967, with the latter arranged in descending order of importance.

**Death registration states only.

Sources: (1) For 1900: U.S. National Office of Vital Statistics, Vital Statistics of the United States, 1950, Vol. 1. (Washington, D.C., 1950) Table 2,26, p. 170.

(2) For 1967: U.S. Department of Health, Education and Welfare, Public Health Service, Vital Statistics of the United States, 1967, Vol. II - Mortality, Part A (Washington, D.C., 1969), Table 1-5, p. 1-6.

FIGURE 1

In particular, the health consequences of smoking are well known. In addition to causing more than 30% of cancers, cigarettes cause enormous amounts of heart and lung disease. Yet the NIH effort relating directly to smoking is very small. The Smoking and Health Program of the National Cancer Institute had a fiscal year 1975 budget of less than $8 million.[13] Yet it is hard to imagine a research finding which could have greater impact on the health of the population than finding a safe cigarette or improving techniques of health education.

[13] National Cancer Institute, "Smoking and Health Program," National Institutes of Health, June, 1975.

The role of psychosocial stressors appears to be seriously underemphasized. As Cassel [14] says, one illustration is the health consequences that follow the disruption of important social relationships, particularly the death of a spouse. "It has been shown that widowers have a death rate three to five times higher than married men of the same age for every cause of death. It is difficult to conceive of a specific etiologic process responsible for the increased death rate from such diverse conditions as coronary heart disease, cancer, infectious diseases and peptic ulcer, and it would appear more reasonable to consider the loss of a spouse as increasing the susceptibility of such men to other disease agents." Yet according to a staff paper from the President's Biomedical Research Panel, NIH only supported $50 million of "social science" research in 1975.[15]

Epidemiological research is also important in the question of research priorities. Much useful information concerning the etiology of such diseases as lung cancer, coronary artery disease, occupationally related cancers and hepatitis has resulted from such studies. The National Institutes of Health *has* funded important epidemiological research in the past, noteably the Framingham study which elucidated the risk factors in coronary artery disease. However, NIH funding at the present is pitifully small, and few institutes have an epidemiology program. This is the case despite a great deal of interest in epidemiological research among the institute directors. Several institute directors stated that they desired a program, but were unable to recruit a good epidemiologist. Comprehensive Cancer Centers are expected to have an epidemiology program, but several have been unable to recruit a director. Good grant proposals for epidemiological research are consistently funded by NIH, but few are submitted. Clearly, the problem is a lack of epidemiologists and institutional resources to support them. Experts in this field made the following suggestions:

1. Ten to fifteen national centers for epidemiology could be developed around the country to serve as foci for research and training.

2. Research career awards could be given to universities to establish professorships in epidemiology. The university would be required to nominate the epidemiologist and to commit institutional resources to a program.

3. The Epidemiology and Disease Control Study Section could be given technical resources to work with those submitting grant proposals. The problem with most grant proposals is that the methodology is unsatisfactory epidemiologically. Yet, the intramural programs in the National Cancer Institute and National Heart and Lung Institute have had good success working with clinicians and others on contract where NIH retains responsibility for the methodology. This mechanism could be expanded.

4. More intramural research monies could be allocated to epidmiology projects. Fields ripe for research include the role of nutrition in heart disease and cancer, the epidemiology of chronic lung disease, and the epidemiology of high blood pressure.

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[14] Cassel, J., "Psychosocial Processes and 'Stress': Theoretical Formulation," *Int. J. Health Serv.* 4: 471–482, 1974.

[15] Staff Report of the President's Biomedical Research Panel, "Federal Funding for Health and Health-Related Research," 1975.

Expectations of Research

The expectations of health research often seem unrealistic. Great cures or changes in disease statistics cannot be expected in the short-run. However, even accepting that research must be viewed as a long-term investment with considerable unpredicability, the question remains as to how quickly it is reasonable for the public to expect evidence of return on its investment and how much evidence is required. Researchers view their productivity in terms of personal success and fulfillment, which does not assure a deep commitment to produce results which aid those who are paying for the research—the general public.

Quite realistically, most thoughtful researchers do not expect great changes in mortality rates to result from research. Man is mortal, and personal health habits and environment have a great influence on health. On the other hand, morbitity and functional status can probably be greatly changed, at least for specific diseases. For example, the National Heart, Lung and Blood Institute has hopes of finding an effective treatment for hemophilia soon, but this will not affect overall mortality statistics, because hemophilia is too rare. On the other hand, it will be of great importance to affected individuals and their families. Improvements in effective functioning and quality of life must not be overlooked when the goals and productivity of biomedical research are assessed.

Finally, without improved statistical systems, assessment of these improvements will not be possible (See Chapter 8).

CHAPTER 2

The Federal Role in Health Research

National support for health research and development totalled an estimated 4.3 billion dollars in fiscal year 1974. Sixty-five percent of this total came from the Federal government, with a total of 2.8 billion dollars, 62% of which was expended by NIH. Private industry was the second largest supporter of health research and development, with an investment of 1.2 billion dollars (27.5% of the total), the majority of which was related to drug development. The remainder, came from State and local governments, voluntary health organizations, private foundations, and other private associations.[16] The $4.3 billion investment in health research and development made up 13.3% of the total societal investment in research and development of $32.1 billion.

Health Research Funds and General Health Expenditures

National health expenditures in 1974 totalled 104.2 billion dollars.[17] The research and development expenditure of 4.3 billion dollars made up 4.1% of that total.

For 1974, the total Federal expenditures for medical and health related activities was approximately 28.4 billion dollars. Thus, approximately 10% of the Federal health dollar supports research and development.

Agencies Participating in Health Research

As noted, Federal funds for health research are channeled principally through NIH, but many other agencies of the Federal government also support health research.

Table 2 shows how the Federal research dollar is divided.

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[16] Office of Program Planning and Evaluation and the Division of Research Grants, National Institutes of Health, "Basic Data Relating to the National Institutes of Health, 1975."

[17] Worthington, N.L., "National Health Expenditures, 1929-1974," *Social Security Bulletin*, 38: 3-20, February, 1975.

TABLE 2.—*Federal outlays for health research by agency, 1975*

[In millions of dollars]

Department of Health, Education, and Welfare (total)	(1, 867)
Health Services Administration	9
Health Resources Administration	58
Alcohol, Drug Abuse, and Mental Health Administration	114
Center for Disease Control	42
National Institutes of Health	1, 598
Food and Drug Administration	27
Assistant Secretary for Health	4
Social Security Administration	
Social and Rehabilitation Service	2
Other HEW	13
Department of Defense	104
Veterans Administration	93
Department of Housing and Urban Development	
Department of Agriculture	47
Environmental Protection Agency	20
National Aeronautics and Space Administration	59
Energy Research and Development Administration	143
Department of Labor	1
Department of State	
National Science Foundation	44
Department of Interior	35
Department of Transportation	15
Department of Justice	
Other agencies	31
Agency contributions to employee health funds	
Total outlays, 1976	2, 459

Source: Office of Management and Budget, "Special Analysis K, Federal Health Programs," February-January 1976, p. 215.

GROWTH OF THE NIH PROGRAM

Prior to World War II, biomedical research in the United States was a small activity, primarily academically-based. During the years following World War II, the field of biomedical research experienced very rapid growth. Research dollars as a proportion of national health expenditures rose from 1.2% in 1952 to 4.0% in 1972, reaching a high of 4.8% in 1966. Table 3 shows NIH appropriations for all grants and research over that 20 year period. From 1950 to 1960, the annual growth rate for all grants was about 80%.

With the introduction and growth of other new Federal health programs, especially the Medicare and Medicaid programs, and the Vietnam War, biomedical research support faced stiff competition. Table 4 shows NIH research grant and contract obligations in constant dollars from 1967, indicating that there was actually a drop in 1970, although there has been a subsequent rise. The end of the rapid growth days helped foster strong political pressures which changed the relative support for the different NIH institutes. Table 5 shows that in 1970, the combined budgets of the Cancer and Heart and Lung Institutes was 34% of the total NIH research budget, but this had climbed to 51% in the President's 1975 budget.

TABLE 3.—NIH APPROPRIATIONS FOR ALL GRANTS AND RESEARCH GRANTS. 5-YR. INTERVALS—1950 TO 1970 AND 1972

[In millions of dollars]

Year	Total grants [1]	Biomedical research grants
1950	26.8	12.3
1955	54.3	30.3
1960	334.4	179.5
1965	875.2	469.5
1970	1,210.3	577.9
1972	1,638.8	717.5

[1] Includes grants for research, fellowships, training, health research facilities, and community mental health centers construction, student loans, community demonstration projects, etc.

Source: "Health Program Memorandum and Discussion of Budget/Legislative Issues, 1976–80," Assistant Secretary for Planning and Evaluation, Department of Health, Education, and Welfare, July, 1974.

TABLE 4.—NIH EXTRAMURAL RESEARCH OBLIGATIONS IN CONSTANT DOLLARS [1967=100] AND PERCENT DISTRIBUTION AMONG INSTITUTES

	Constant Dollars					
	1967	1970	1973	1974	1975	House 1976
NIH total	100	88	118	146	160	161
Cancer	100	89	195	248	275	269
Heart/lung	100	82	129	165	146	151
All other NIH	100	89	96	115	136	140

Source: "Health Transition Papers," Assistant Secretary for Plannning and Evaluation, July 1975.

TABLE 5.—PERCENTAGE DISTRIBUTION OF NIH RESEARCH SUPPORT

	1970	1973	1974	Present 1975	House 1975
NIH total	100	100	100	100	100
Cancer	18	29	3	34	33
Heart/lung	16	18	17	17	16
All other NIH	67	54	53	49	51

Source: "Health Program Memorandum and Discussion of Budget/Legislative Issues, 1976–80," Assistant Secretary for Planning and Evaluation, July 1974.

CHAPTER 3

History and Growth of the National Institutes of Health

In order to appreciate problems now facing NIH, it is helpful to begin with the history and growth of the institution.

The National Institutes of Health had its origins in 1887, when a research laboratory was founded at the Public Health Service Marine Hospital, Staten Island, New York. In 1891, this was renamed the Hygienic Laboratory, and moved to Washington, D.C. In 1930, the Hygienic Laboratory was renamed the National Institute of Health. While during this early period the research efforts were primarily directed toward infectious diseases, the NIH was established "for the special purpose of pure scientific research, to ascertain the cause, prevention and cure of diseases affecting human beings." [18] Following the establishment of the NIH, the focus of study shifted and chronic disease began to be emphasized. The Surgeon General stated in 1937 that "the acute infectious diseases have declined rapidly under the impact of public health efforts." But he noted that there had been a concomitant increase in many of the diseases of adult life, particularly the chronic diseases, and made a commitment to a shift in emphasis to the prevention and treatment of the chronic diseases.[19] That year, Congress authorized the National Cancer Institute and the first research grants were made.

The NIH research program had originally been intended to be only an intramural ("within the walls") research program. The Senate report accompanying the Act establishing the National Institute of Health stated: "The plan of the Institute is to make of it a great cooperative science organization in which leading experts in every branch of science will be brought together and given an opportunity to work in unison for the purpose of discovering all the natural laws governing human life, and especially to learn those variations of such laws which are detrimental to human health. It is commonly believed that if there is brought together in one central plan under one directing head the very ablest experts in the sciences of medicine, surgery, chemistry, physics, biology, bacteriology, pharmacology, pharmacy, dentistry, etc., and a concentrated united effort for a term of years is made by them against diseases, singling out first the more important maladies such as cancer, tuberculosis, common colds, pneumonia, etc., its success will result therefrom." [20] However, NIH diverged from this concept as a singular approach and sought authority to expand its grants program, which was allowed in the Public Health Service Act of 1944.

Section 301 of that Act empowered the Surgeon General to "make grants-in-aid to universities, hospitals, laboratories and other public

[18] Senate Reporter No. 1280, 70th Congress, First Session, Page 2.
[19] Annual Report of the Surgeon General of the Public Health Service of the United States, 1937, Page 14.
[20] Senate Report No. 102, 71st Congress, Second Session.

and private institutions and to individuals in carrying out the general purposes of conducting research relating to the causes, diagnosis, treatment, control and prevention of physical and mental diseases and impairments of man." In December, 1945, forty-four wartime research contracts were transferred to Public Health Service jurisdiction, giving sufficient funds for a general extramural research program administered by the NIH. In 1946, a research grants office was created at the NIH to administer these projects and to operate a program of research grants and fellowship awards. And in 1947, the Division of Research Grants was established, and the first training grants were awarded.

In 1947, the Surgeon General predicted that "new programs should emerge from the blueprint stage and all peacetime health services promise to gather increased momentum. As the country's health workers speed their attack on vital problems, particularly those related to chronic disease or old age, wide public support may be anticipated. Never before has there been such keen and widespread interest in health matters throughout the land." [21] This was rapidly followed by the establishment of the National Heart Institute in 1948 by the National Heart Act, which changed the name of the National Institute of Health to the National Institutes of Health. That same year, the National Dental Research Act authorized the National Institute of Dental Research, the National Microbiological Institute and the Experimental Biology and Medicine Institute were established. Other institutes were added in the years that followed. In 1949, the National Institute of Mental Health was established, and in 1950 the Omnibus Medical Research Act authorized the National Institute of Neurological Diseases and Blindness and the National Institute of Arthritis and Metabolic Diseases, the latter absorbing the Experimental Biology and Medicine Institute. The Act also gave the Surgeon General authority to establish new institutes.

It can be noted from this history that the various institutes established did not follow a consistent pattern in their naming, that is, by disease or organ system. However, NIH has historically been referred to as having categorical institutes, implying a certain discipline in organization logic.

In 1953 the Clinical Center opened amid considerable dispute between laboratory scientists and clinicians. The latter were convinced of the necessity of a clinical dimension; the former were convinced it would dilute the research effort. However, the dilution did not occur. The Clinical Center, with laboratories and corridors adjacent to hospital rooms, became the prototype for many other research hospitals, and many have felt that the dynamics between clinical care and medical research have been the major strength of NIH over the years.

In 1955, the National Microbiological Institute was renamed the National Institute of Allergy and Infectious Diseases.

In 1956, the Health Research Facilities Act established a program of matching grants for research construction in non-Federal institutions, which was administered by the newly-established Division of Research Facilities and Resources.

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[21] Annual Report of the Surgeon General of the Public Health Service of the United States, 1947, Page 269.

In 1958, the Division of General Medical Sciences was established to extend medical research into diseases and other dimensions of biomedical research not being investigated by other parts of NIH.

In 1962, the National Institute of Child Health and Human Development was authorized and the Division of General Medical Sciences was renamed the National Institute of General Medical Sciences. That same year, the National Library of Medicine moved to the NIH campus in Bethesda, Md.

The Heart Disease, Cancer and Stroke Amendments of 1965 authorized regional medical programs to combat those three diseases. The Division of Regional Medical Programs was established in NIH the following year to administer grants under these amendments. Three years later, in 1968, the Division of Regional Medical Programs was transferred to the Health Services and Mental Health Administration of the Department of Health, Education, and Welfare (DHEW).

In 1966, the Division of Environmental Health Sciences was established.

In 1967, the National Institute of Mental Health was separated from NIH and became a separate agency of the Public Health Service. The intramural research program of the Institute, however, continued to be located on the NIH campus.

In 1968, NIH became an operating agency within DHEW, and the Bureau of Health Manpower and the National Library of Medicine became components of NIH. That same year the John E. Fogarty International Center for Advanced Study in the Health Sciences was established along with the National Eye Institute. The National Institute of Neurological Diseases and Blindness became the National Institute of Neurological Diseases and Stroke.

In 1969, the Division of Environmental Health Sciences became the National Institute of Environmental Health Sciences. That same year, under the pressure to expand research activities into lung diseases, the National Heart Institute was redesignated as the National Heart and Lung Institute; and in 1976 was remaned the National Heart, Lung, and Blood Institute.

In 1971, the National Cancer Act of 1971 authorized the National Cancer Program, enlarged the authority of the National Cancer Institute and established a National Cancer Advisory Board. As previously noted, this followed a period of shrinking support for biomedical research. It was followed by a period of drastically restricted growth, and even reductions in support, for the other institutes. At that time, the Senate-passed bill called for an independent "Conquest of Cancer" agency, but the House bill kept the effort within NIH.

In 1972, a National Sickle Cell Anemia Control Act established a national program for the diagnosis and treatment of, and counseling and research in, Sickle Cell Disease. Also, the National Institute of Arthritis and Metabolic Diseases was renamed the National Institute of Arthritis, Metabolism and Digestive Diseases. The National Heart, Blood Vessel, Lung and Blood Act expanded the authorities of the National Heart and Lung Institute to intensify the national effort against heart, lung, and blood diseases. The National Cooley's Anemia Control Act authorized additional funds for research on Cooley's Anemia.

In 1974, the National Cancer Act Amendments of 1974 permitted additional Comprehensive Cancer Centers, required peer review of contract projects just as had traditionally been applied to grant applications, and called for a more effective world-wide dissemination of cancer knowledge. These amendments also established the President's Biomedical Research Panel to review research programs conducted by NIH and by the Alcohol, Drug Abuse and Mental Health Administration and to recommend policy regarding their operation. In addition, the National Research Act of 1974 established the National Commission for the Protection of Human Subjects of biomedical and behavioral research. The Research on Aging Act authorized establishment of the eleventh institute at NIH, the National Institute on Aging. Finally, the Sudden Infant Death Syndrome Act authorized the National Institute of Child Health and Human Development to carry out sudden infant death syndrome research.

In 1975, the National Institute of Neurological Diseases and Stroke was renamed the National Institute of Neurological and Communicative Disorders and Stroke.

So at the present time, the National Institutes of Health is made up of the following institutes, with their dates of origin:

National Cancer Institute	1937
National Heart, Lung, and Blood Institute	1948
National Institute of Allergy and Infectious Diseases	1948
National Institute of Dental Research	1948
National Institute of Neurological and Communicative Disorders and Stroke	1950
National Institute of Arthritis, Metabolism, and Digestive Diseases	1950
National Institute of General Medical Sciences	1958
National Institute of Child Health and Human Development	1962
National Institute of Environmental Health Sciences	1966
National Eye Institute	1968
National Institute on Aging	1974

History of the Department of Health, Education, and Welfare in Relation to NIH

The National Institutes of Health has been a part of the Public Health Service from its earliest beginnings.[23] The Public Health Service was transferred to the new Federal Security Agency from the Treasury Department in 1939.[24] In 1953, the Department of Health, Education, and Welfare was formed from the Federal Security Agency, making the Secretary of HEW a Cabinet post for the first time. At that time, HEW had 34,000 employees with a total expenditure of $5.4 billion. The NIH appropriation that year was $59,031,000,[25] a rise from less than $3 million in 1945.[26] However, as pointed out in Chapter 2, the NIH appropriation grew rapidly.

Table 6 demonstrates the rapidity of the growth in comparison to other Federal health care expenditures. By 1965, NIH had grown so fast that it made up more than 37% of the Federal health effort. NIH staff are fond of recalling those days, when the agency made up a very large and ever-growing part of the Federal health dollar. If it is a morale problem at NIH, it may be traced in part to the difficulty which staff who were employed there during this period have had in adjusting to this change in status.

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[23] Strickland, S. P., *Politics, Science, and Dread Disease*, Cambridge, Mass., Harvard University Press, 1972.
[24] Miles, R. E., *The Department of HEW*, Washington, Praeger, 1974.
[25] *NIH Almanac 1975*, National Institutes of Health, DHEW, p. 106.
[26] Miles, *op. cit.*

TABLE 6

Year	Federal health care Expenditures[1] (millions)	NIH appropriation[2] (millions)	Percentage
1955	$1,583	$81.3	5.1
1960	2,102	430.0	20.4
1965	2,840	1,059	37.2
1967	[3] 7,471	1,413	18.9
1970	13,403	1,523	11.4
1973	20,182	2,497	12.4

[1] Worthington, N. L., "National Health Expenditures, 129–74," Social Security Bulletin 38: 3–20, 1975.
[2] NIH Almanac 1975, National Institutes of Health, DHEW, p. 106.
[3] The great expansion was primarily due to titles 18 and 19 of the Social Security Act, medicare and medicaid.

The position of an Assistant to the Secretary for Health and Medical Affairs was established at the same time as the Department of HEW. This position was renamed "Assistant Secretary" about 1966, but was purely a staff function until 1968, when the Assistant Secretary was converted into a line officer responsible for the health-oriented agencies of HEW, including NIH. The Public Health Service is presently composed of six agencies, the Health Services Administration, the Health Resources Administration, the Alcohol, Drug Abuse, and Mental Health Administration, the Food and Drug Administration, the Center for Disease Control, and the National Institutes of Health. During the 1973 to 1975 period, Dr. Charles Edwards, the then-Assistant Secretary of Health, increased the size and operational influence of this office, creating a layer of management which had been non-existent or of limited power until then. The evolution of the Assistant Secretary of Health as a potent influence in the management of the Public Health Service, and of NIH in particular, has been an extremely sensitive development at NIH, as it has enjoyed autonomy for the majority of its existence.

Recent Leadership at the NIH

Dr. James Shannon was Director of NIH from 1956 to 1968. The story of his effective leadership is well-known.

Dr. Shannon was succeeded by Dr. Robert Z. Marston, whose tenure as NIH Director was associated with the growth of the influence of the White House in the management of biomedical research.[27] Dr. Marston's directorship was abruptly ended, without a full public explanation, by his dismissal shortly after the 1972 elections.

Dr. Marston was succeeded by Dr. Robert Stone. Dr. Stone's tenure was weakened by the resignation of his experienced Deputy Director, Dr. John Sherman in early 1974, and of his respected Deputy Director for Science, Dr. Robert Berliner, in late 1973. Dr. Stone's directorship also ended abruptly with his dismissal on January 31, 1975. Both Dr. Marston's and Dr. Stone's tenures as NIH Director saw an extraordinary exodus of the most senior level staff members—a group essentially assembled under Dr. Shannon—and felt by observers of the agency to be one of its greatest sources of strength. The dismissal of two directors in a little more than two years and the exodus of the senior staff shocked the biomedical

[27] Culliton, B. J., "Health Hierarchy: Marston Fired and He's Not the Only One," *Science*, 178: 1268–1270, December, 1972.

research community, adding to the worsening budgetary picture which already had it concerned.

On July 1, 1975, Dr. Donald Fredrickson became Director of NIH. Dr. Fredrickson had been Director of the National Heart Institute in the 1960's, but had left NIH to become President of the Institute of Medicine. Following two NIH directors appointed from outside the NIH community, the appointment of a respected former NIHer was well received within the troubled agency. Almost simultaneously, Dr. Theodore Cooper, then Director of the National Heart and Lung Institute, became Assistant Secretary of Health.

Summary.—The post-war history of NIH reveals rapid growth, leveling off in the late 1960's. Coincident with this leveling has been the greatly expanded growth of other Federal health activities, especially financing of health care of the aged and the indigent. This latter development, accompanied by inflation and pressures for even greater attention to health service needs, has led to pressures to both stall NIH funding growth prospects and even to shift funds from research into service areas.

CHAPTER 4

The Mission of the National Institutes of Health

NIH has described its mission as to advance the health and well-being of man through:

1. Enlarging knowledge and understanding of the normal and pathological processes of the human body, and
2. Developing ways in which the providers of medical care can safely and effectively intervene to prevent, treat or cure diseases and disabilities.[28]

This mission has essentially meant *knowledge development* without a corresponding commitment to *knowledge application*. The former emphasis has continued in the mission described for NIH in the HEW long range planning documents.[29]

NIH has classically pursued this mission through supporting:

(1) Biomedical research and development, including in some instances demonstration and control.

(2) Research training.

(3) Development of research resources.

(4) Communication of the findings and results of the research.

However, NIH has come under increasing pressure, especially from the Congress, to expand its role into heretofore uncovered areas or to selectively expand certain efforts in which it already has some activity. NIH has seen itself and has been seen by the Congress and by the Department of HEW as a focus of excellence and as a basic resource. While appreciating this, NIH spokesmen are concerned about specific proposals for change as well as about the effects of overly rapid change.

Within NIH, its own leaders have been grappling with the issue of mission. In fact, two institute directors recently proposed a new missions statement that emphasizes the prevention of disease and disability.[30] To accomplish this, NIH would:

(1) Expand the base of scientific knowledge in the biomedical sciences and other disciplines relevant to the improvement of health through conduct and support of:

(*a*) Studies in the basic life functions and the epidemiology, etiology, pathogenesis and natural history of disease;

(*b*) Applied clinical and field research in disease prevention and control; and

(*c*) Research into the technological and sociological aspects of health care delivery for specific diseases or groups of disorders.

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[28] "The National Institutes of Health Forward Plan, Fiscal Years 1977-1981," April 30, 1975.
[29] "The Forward Plan for Health, Fiscal Year 1976-80," DHEW, Office of the Assistant Secretary for Health, June, 1974.
[30] Kupfer, C. and Kretchmer, N., "New Missions Statement for NIH," NIH Memorandum, April 2, 1975.

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2. Support research training in the basic and clinical sciences.

3. Evaluate the application of research findings and technological advances in biomedicine through:

(*a*) Design and support of controlled clinical trials; and

(*b*) Development and short-term operation of demonstration and control programs to evaluate the applicability of new research knowledge and specific disease problems.

4. Foster application of research finding through:

(*a*) Coordination and integration of research efforts with other Federal agencies including those that are service oriented;

(*b*) Dissemination and exchange of scientific and technological information, within the nation and abroad, in medicine, health and related fields, including the support of workshops and other educational activities for health care providers and the development and support of medical libraries; and

(*c*) Development and coordination of national programs of health education for the public related to these disorders.

5. Initiate and cooperate in government-wide efforts to resolve special and national health problems, including those which may require emergency action.

6. Provide scientific consultation to Federal and non-Federal organizations in the development of new programs to improve the nation's health.

7. Develop and formulate policies concerning human experimentation and other important issues related to the conduct and support of biomedical research.

8. Support the development of research resources.

Dr. Kupfer, Director of the National Eye Institute, and Dr. Kretchmer, Director of the National Institute of Child Health and Human Development, point out that NIH is the largest reservoir of expertise dealing with categorical disease issues in the Federal government. It seems to them only natural that the NIH should be called upon for assistance in the *implementation* and *operation* of new Federal health programs. In particular they refer to the continuum of health activities from fundamental research at one end to the treatment of patients at the other. The middle area of this continuum includes control, demonstration, and health education programs. They recognize that some of their colleagues at NIH consider these activities to be outside the traditional bounds of NIH responsibility. Drs. Kupfer and Kretchmer ask only that the new control evaluation, demonstration, and education programs be given their own additional resources.

Demonstration and Control Programs

The area of demonstration and control is of particular concern to NIH staff. The Director of NIH defined these terms as follows: demonstration means either showing that something works, such as patient education, or showing that something that works in an ideal setting works in a practical field setting. Control has as its goal the reduction of disease, preferably by prevention, and is the ultimate objective of biomedical research. However, its meaning has changed to refer to the extension or diffusion throughout the health care system

of an intervention, technology or some other change in the substance of medical practice.[31]

Demonstration and control programs are not a new NIH activity, but date from the National Cancer Institute Act of 1937. In 1946, the Cancer Control Branch was established within the National Cancer Institute to provide grant-in-aid support to state health agencies for cancer control activities. As new institutes developed at NIH, additional control activities were formed. In the early 1960's the control programs of NIH were transferred to the then Public Health Service Bureau of State Services, and in 1968, these programs were phased out and some components were transferred to the Regional Medical Programs. Thus, the new demonstration and control activities in cancer and heart disease mark the return of control programs to NIH. The National Arthritis Act of 1974 and the National Diabetes Mellitus Research and Education Act have extended the thrust of control programs to other disease areas, although the diabetes activity was assigned by the Department of HEW to the Center for Disease Control.

Kupfer and Kretchmer [32] recognize that some institutes have corresponding service delivery programs to which they can relate their research. In those cases, the problem is one of coordination and communication. Examples of this are the National Institute of Allergy and Infectious Disease and its corresponding agency, the Center for Disease Control, or the National Institute of Child Health and Human Development and the Maternal and Child Health Program. However, there are a variety of demonstration and control programs already being carried out by NIH when there is no corresponding service activity. Examples of those are as follows:

1. National Cancer Institute—the Cancer Control Program which in 1974 funded major activities in the fields of prevention, screening, diagnosis, treatment, rehabilitation, and education.
2. National Institute of Allergy and Infectious Disease—vaccine development.
3. National Institute of Neurological and Communicative Disorders and Stroke—programs to determine better methods for the management of acute spinal cord injury and stroke intensive care, which includes research into systems of care delivery in addition to research directed toward improved therapy.
4. National Heart and Lung Institute—prevention, education, and control activities within each of the three major programs of the National Heart and Lung Institute, such as the National High Blood Pressure Education Program.
5. National Institute of Dental Research—National Caries Program.
6. National Institute of Arthritis and Metabolic and Digestive Diseases—artificial kidney, the Chronic Uremia Program.
7. National Institute of General Medical Sciences—research into the most effective treatment for burn victims.

Actually, several institute directors whose programs do not presently involve demonstration and control programs expressed interest in developing such programs. The general orientation at NIH, how-

[31] Fredrickson, D., Testimony Before the President's Biomedical Research Panel, November 24, 1975.
[32] Kupfer and Kretchmer, *op. cit.*

ever, is that demonstration and control programs should involve the establishment of *innovative* disease control technology through *controlled, time-limited* projects conducted in limited populations.

A general attitude found rather consistently throughout NIH is that a new technology must be proven by a proper demonstration, preferably a controlled clinical trial. Furthermore, once it is demonstrated successfully, it should be available to the entire population through the service system. The latter is clearly not the role of NIH. It is also apparent that the state of knowledge in many disease areas is not ready for organized interventions with the reasonable possibility of success. Decisions must be made on a disease-by-disease basis. Examining the institutes, it is observed that not all support demonstrations of new technology which may suggest a problem in need of resolution by NIH management. Demonstration and control already makes up as much as $75 million a year of NIH activities,[33] and seems certain to grow as an activity.

One demonstration and control program, the Comprehensive Cancer Centers, was looked at in some detail. The Cancer Centers Program of the National Cancer Institute was initiated in the early 1960's in response to a need for inter-disciplinary cancer research and rapid translation of new research findings into coordinated care for cancer patients. A trend toward a broader scope in the centers was reinforced by the National Cancer Act of 1971, which called for the establishment of 15 new Comprehensive Cancer Centers. The renewal of the Cancer Act in 1974 made provision for additional Comprehensive Cancer Centers. There are presently 17 such centers, which were funded at a level of $26 million in fiscal year 1975, including some which are not comprehensive. The Comprehensive Cancer Centers are encouraged to compete for resources from other parts of the Cancer Institute, and the 17 such Centers were able to gain a total amount of NIH support of approximately $115 million dollars in fiscalyear 1975.

The Comprehensive Cancer Center is required to have the following characteristics:

> "1. The Center must have a stated purpose that includes carrying out the basic and clinical research, training in and demonstration of advanced diagnostic and treatment methods relating to cancer.
>
> 2. The Center must have high quality interdisciplinary capability in the performance of diagnosis and treatment of malignant diseases.
>
> 3. The Center must have an environment of excellence in basic science which will assure the highest quality in basic research.
>
> 4. The Center should have or should develop an organized cancer detection program.
>
> 5. The Center must maintain a statistical base for evaluation of the results of its program activities. For this purpose records should be developed which will standardize disease classification to enable exchange of information between institutions.
>
> 6. The Center should provide leadership in developing community programs involving active participation by members of the medical profession practicing within the area served by the Center.

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[33] Fredrickson, *op. cit.*

7. The center must have a strong research base (fundamental and applied) and related training programs, with an organizational structure which will provide for the coordination of these activities with other facets of the center program.

8. The Center will participate in the National Cancer Program by integrating its efforts with the activities of other centers in an integrated nationwide system for the prevention, diagnosis and treatment of cancer. For this purpose the Center must have sufficient autonomy to facilitate this function.

9. The Center must have an administrative structure that will assure maximum efficiency of operation and sound financial practices . . . (and) will have the authority to establish the necessary administrative and management procedures for carrying out its total responsibility as defined in the criteria.

10. It is a requirement that each Center group sufficient beds for cancer patients to give the program cohesion, identification and favorable facilities for the clinical research program to be carried out. In general it is expected that existing inpatient facilities will be committed for this purpose." [34]

There have been allegations that the Comprehensive Cancer Centers—the first of which was designated in 1972—are not adequately disseminating the latest information concerning cancer to the public and to the practicing community. The basic mechanism used by the Centers for communication to the practice community is through forming relationships with nearby community hospitals. Several Centers have already had remarkable success in achieving such a network, and all show evidence of moving in that direction. In terms of communication with the public, the National Cancer Institute is presently letting contracts, through the Division of Cancer Control and Prevention, to develop toll-free information lines for both medical practitioners and the public at each Center. Given the early nature of this program, there is natural sensitivity to the problem of effectiveness of communication, and adequate attempts are being made to address it. Likewise, efforts have been made to develop mechanisms for the directors and other staff of the Centers to communicate among themselves.

There are, however, problems with this program. The Yarborough Committee on Consultants [35] recommended the Comprehensive Centers as the focus of a network of cancer resources. However, the Centers have no authority for functioning as a focal point in an area; thus, much of the rationale has been lost. Although the Comprehensive Centers have been successful in competing for funds, large amounts of money go to other institutions in the same area and these independent programs are not always well-coordinated.

The basic problem seems to be one of philosophy. Should the Centers be regional resources or high-quality research institutes? The competitive mode of granting is not fully consistent with developing regional resources. For example, one Comprehensive Center had total awards of about $297,000 for the two years 1974 and 1975, while other Centers have support of $10 million and more. Geographic location

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[34] National Cancer Institute, "Cancer Centers Program," Information and Guidelines on Cancer Center Support Grants, National Institutes of Health, June 1973.

[35] U.S. Congress, Senate Committee on Labor and Public Welfare, *National Program for the Conquest of Cancer*, Report of the National Panel of Consultants on the Conquest of Cancer, 91st Congress, Second Session, November, 1970.

of the Centers has not been optimal either. A study carried out by the National Cancer Institute shows it is possible to optimize population access to Centers,[36] but the expected designation of Centers in New York City and Los Angeles, areas which already have Centers, shows how the free enterprise philosophy inherent in the grants approach prevents optimal distribution of these important resources.

Another problem is that few Centers actually meet all the criteria; according to the General Accounting Office, stated intention to meet the criteria is often sufficient.[37] One of the most important shortcomings is in the area of data collection and analysis. Few Comprehensive Centers have an epidemiologist, and individuals who have site-visited Centers report that where epidemiologists are present they are not central to the functioning of any Center. This relates partially to the shortage of epidemiologists mentioned in Chapter 1. A related problem is that the Comprehensive Centers have no common data base to allow exchange of information, provide a basis for standardization of comparisons, etc., although one is being developed. This data base, however, will not include information useful for epidemiological studies, and an important resource for research into etiology will be lost. It seems that the Cancer Institute should have insisted on a common data base from the beginning of the designation of the Centers.

Directors of several of the Comprehensive Centers were contacted, and one made available the preliminary results of a survey of the directors of all centers. Perhaps the greatest problem identified by the directors themselves was the question of the role of the Comprehensive Centers, particularly in relation to the National Cancer Institute. Comments such as this were common: "The relationship of the other divisions at the National Cancer Institute to the Division of Research Resources and Centers seems to be minimal." A second problem identified by the directors was that of evaluation. Several directors stated that the guidelines and goals for centers were far from clear and that specific goals are urgently needed.

Finally, several directors of specialized cancer centers or institutes receiving large amounts of cancer research funds have pressured the National Cancer Institute to loosen its criteria so that they could become Comprehensive Cancer Centers. The leadership of the National Cancer Institute deserves credit for resisting this challenge and in requiring a strong multi-disciplinary team with a powerful director, a team which cuts across such institutional barriers as traditional departments of a medical school. There may be dangers in a separate cancer treatment system, but it seems clear that if the research and outreach activities of the Comprehensive Cancer Centers are to be successful, they must involve a team of professionals ranging from clinical physicians to epidemiologists to chemists. If an institution is not willing to make this possible, the National Cancer Institute is correct in not designating it as a Comprehensive Cancer Center.

The Cancer Control Program, which was established in 1971 under the National Cancer Act, deserves a few words as well. Cancer Control

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[36] Ellwein, L. B. and Kalberer, J. T., "Optimal Locations of Cancer Centers on the Basis of Population Access," *Fed. Proc.* 34: 1411–1416, May, 1975.

[37] United States General Accounting Office, "Comprehensive Cancer Centers: Their Location and Role in Demonstration," Washington, D.C., March 17, 1976.

conducts most of its activities through contract. As such it is a prime target for criticisms by those in the biomedical field who believe that contracts are a naturally lower quality mechanism of support than the peer-reviewed grant. Irrespective of the funding mechanism utilized, as a Congressionally-mandated activity, this program will need careful evaluation.[38] Such evaluation can only be done after a reasonable period of operation, such as two to five years from now, when the program should begin to show results. It may be commented here, however, that careful thought has gone into the development of the program thus far.[39] It is also worth noting that 36% of the Cancer Control budget went to Comprehensive Cancer Centers in 1974.

From the preceding discussion it seems clear that the National Cancer Institute has certain problems associated with its centers and control programs—such as the coordination of activities within a single region. These problems will deserve careful and detailed management attention as a high priority matter.

The program of National Research and Demonstration Centers in the National Heart, Lung, and Blood Institute was also examined, but to a much more limited extent than in the case of the National Cancer Institute. The National Heart, Blood Vessel, Lung and Blood Act of 1972 provided for the development of up to 15 such centers for problems related to heart, blood vessel, and blood diseases, and up to 15 centers for problems related to chronic lung diseases. The announcement of the program was released in August 1973, and in the spring of 1974, out of 47 applications, three such centers were chosen, one in heart and vascular diseases, one in lung diseases, and one in blood resources. While the leadership of the Institute would like to implement the program, particularly in light of Congressional intent that they do so, with the shortage of discretionary funding, and with other mandates such as hypertension and sickle cell anemia, expansion of this program will go slowly.

Clinical Trials at the National Institutes of Health

Clinical trials represent another important part of the spectrum which ranges from basic research to general application in medical practice. They could be said to come after clinical investigation and before demonstration and control projects. A clinical trial is a scientific research activity undertaken to prospectively define the effect and value of prophylactic, diagnostic or therapeutic agents, devices, regimens, procedures, etc., applied to human subjects. Clinical trials are an exceedingly important activity in assuring that new procedures, technologies and so forth are indeed useful and helpful before they find their way into general medical practice. This is also important for procedures used in present day medical practice; an observer of the medical practice scene has estimated that only 10–20% of procedures used in present medical practice are proven to be useful by controlled clinical trials.[40]

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[38] "NCI Control Program Should Stay Away from Model Health Delivery, Warns Schmidt; Concentrate on Technology Transfer, Education," *Drug Res. Rep.* 18: 10–11, July 9, 1975.

[39] National Cancer Institute, "National Cancer Control Program Planning Conference," National Institutes of Health, September, 1973.

[40] White, K. L., "International Comparisons of Health Services Systems," *Milbank Mem. Fund Quart.* XLVI: 117–125, 1968.

NIH is deeply involved in clinical trials. (The Food and Drug Administration of DHEW has responsibility for assuring efficacy and safety of drugs, and does this through trials which it terms "clinical investigations".) A recently completed inventory of clinical trials [41] reveals that in 1974 NIH supported 1080 clinical trials costing approximately 168 million dollars. The total cost of these trials from initiation to completion is estimated to be $848 million, with about 40% of that total having been obligated through 1974. About 65% of these studies incorporate controls in their experimental design. It is clear that properly designed and well-conducted clinical trials require major resource investments, are very expensive, and require long periods of time to obtain reliable results.

NIH has increased its support for clinical trials dramatically in the last few years. For example, the total obligations of four institutes, National Cancer Institute, National Heart and Lung Institute, National Institute of Neurologic and Communicative Disorders and Stroke, and the National Eye Institute, increased by 2.85 times in the interval 1971 to 1974. The National Heart and Lung Institute has kept detailed records of its investment in clinical trials over the years, and they are shown in Table 7.

It is impossible to say how much investment in clinical trials at NIH is appropriate; however, this is an extremely important and potentially remunerative investment since it can prevent new unproved procedures from finding their way into medical practice. While the applicability of controlled trials is normally associated with *new* procedures or technologies, there is a significant potential for savings through the evaluation of procedures or technologies already in use. The potential payoff through the deterrence of new and the removal of old ineffective procedures or technologies to the Federal financing programs (Medicare and Medicaid) is considerable. By way of an example of such a situation, the National Eye Institute has begun a trial of early vitrectomy. In this procedure, the vitreous humor of the eye can be removed in diabetics after bleeding into the vitreous occurs and this can often restore considerable vision. This has raised the question whether early vitrectomy at the time of the first bleeding episode might not be even more helpful. The equipment to do the vitrectomy costs about $10,000, ancillary equipment perhaps $50,000. In addition, the operating room nurses will have to be specially trained, there will be a charge for the operation of one to two thousand dollars, and a hospital stay of 7–10 days. There are an estimated 140,000 diabetics eligible for the operation this year, as well as others without diabetes. Multiple operations are often needed on the same person. It is clear that this operation could consume an enormous amount of money. Fortunately, however, the early vitrectomy is now being assessed by a controlled clinical trial *before* it enters general medical practice. The hope of the National Eye Institute is that it may not be paid for under government health programs until and if it is proven to be effective.

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[41] National Institutes of Health, "NIH Support of Clinical Trials," Report to the Acting Director, NIH, May 16, 1975.

TABLE 7.—*Obligations by NHLI for major clinical trials 1963–74*

(thousands of dollars)

1963	2,747	1969	6,367
1964	3,663	1970	6,151
1965	3,327	1971	11,843
1966	3,993	1972	19,445
1967	5,839	1973	22,394
1968	6,584	1974	40,616

In addition to the above considerations, it should be noted that such technology can lead to enormous profits for private companies. In some cases the prospect exists that the National Institutes of Health may do the research and development task from which private companies can then profit. In such instances, it seems appropriate that NIH derive some financial support from such companies. In addition, the potential savings for government health programs seems to make it sensible that if biomedical research funding constraints continue that Medicare and Medicaid could invest a small percentage of their budgets in NIH clinical trials in view of the direct potential for benefit to them.

DISSEMINATION OF RESEARCH RESULTS

Along with the responsibility to develop and evaluate new biomedical knowledge, NIH has an implicit responsibility to disseminate information about health to the public and to the professional community in an effective and timely manner. Congress has shown a particular interest in this aspect of NIH's charge by making special provisions in the National Cancer Act of 1971, and in the National Heart, Blood Vessel, Lung and Blood Act of 1972, for public and professionally-oriented information programs. The recent Arthritis and Diabetes Acts have also stressed dissemination of information.

The persistence of the Congress with regard to effective dissemination of biomedical knowledge by NIH reflected both a feeling of its importance and a criticism of NIH's less-than-vigorous efforts in the past. Communications had previously not been associated with a very high priority. Traditional scientific communication processes were assumed to be both appropriate and adequately effective.

In September, 1974, the Director of NIH established a Committee on Dissemination of Research Results to review this process and develop specific recommendations for a plan of action. The report of the Committee was accepted by the Acting Director in 1975,[42] and formed the basis of a plan of action. The report suggests approaches to improving the communication of research information to each of the major target audiences: research scientists, practicing physicians and other health professionals, and the general public.

In the area of scientist to scientist communication, the plan recognizes that formal communication takes place principally through the more than 2,200 scholarly and scientific journals in which reports of biomedical research are published. This mechanism, which includes critical review of the results as a condition of publication, safeguards the scientific community against widespread dissemination of incorrect

[42] National Institutes of Health, "A Review of Present Practices of NIH in Disseminating Research Findings," March 7, 1975.

information. This traditional mechanism is judged to be generally quite effective. The plan identified, however, a strong need for the continued refinement and expansion of existing systems for storage and retrieval of research data, and for the development of new methods which will improve the scientists access to such material. The National Library of Medicine has been a pioneer in developing such systems and should be expected to play a major role in the future. There is evidence that the institutes have not worked as closely with the National Library of Medicine as they could have.

In the area of communication of research findings to health practitioners, a different problem is found. A busy practitioner would be inundated by the sheer volume of information, if the full output of published results were channelled to him. For this reason, it is essential that there be a sorting-out process and that communication efforts be concentrated on the relatively small portion of current research output which is ready for use by the health professional in patient care. NIH does sponsor a variety of seminars and meetings for practicing physicians, prepares and distributes publications for use of such physicians, and supports control and demonstration programs and the general clinical research centers which function in this regard. In addition, the Lister-Hill National Center for Biomedical Communications conducts and supports the continuing research program to improve the effectiveness and efficiency of biomedical communication.

The NIH information plan commits it to four specific actions to improve communication of new knowledge to the health professional: (1) the NIH will initiate studies to test the feasibility of establishing regional information centers to promote comprehensive telephonic consultative service for practicing health professionals, based on existing academic health centers and networks of NIH supported categorical disease centers. Such contracts have already been let to comprehensive cancer centers to develop information networks. (2) The NIH will prepare and publish in media widely used by physicians and other health professionals a brief monthly review of advances in medical knowledge selected on the basis of their current clinical significance. (3) NIH will take all necessary steps to use new communication technology, including the communication technology satellite (CTS). (4) The NIH will increase support for the National Library of Medicine to expand the National Biomedical Communication Network.

In the coming months more specific proposals will be made by NIH for increasing the support of the Lister-Hill National Center for Biomedical Communication and the National Medical Audio-Visual Center as a means for improving the dissemination of information produced through biomedical research. These proposals will be awaited with interest.

Finally, it is essential that research results be communicated to the public since advances in knowledge often concern health practices or preventive measures, which may be applied by the individual without the help of a health professional. NIH has made a commitment to increase the output of health education information for use by the mass media. The commitment to merely disseminating more information may not achieve the desired effectiveness, however, unless more is learned about the "how" of communicating to the public. In this regard, the National Institutes of Health may also

need to support more research related to health education, both through the National Library of Medicine and through the institutes.

To promote and facilitate improvements in the communication process, a permanent central unit is being established within the office of the Director of NIH. This unit will be responsible for stimulating, coordinating, and evaluating the agency's efforts in dissemination of research results. A permanent committee on communications made up of senior clinically-oriented scientists representing each of the constituent institutes will be formed. In addition, NIH proposes to establish an external advisory group to include scientists, health professionals, communications experts, representatives of other Federal communications programs, and public representatives. NIH also recognizes that cooperative efforts with other Federal and non-Federal agencies in disseminating results could be effective. In particular, the new channels which will be provided through Professional Standards Review Organizations, Area Health Education Centers, the Bureau of Health Planning and Resources Development, and the Food and Drug Administration will be more and more important. Finally, NIH intends to conduct a series of national workshops on the broad subject of research information dissemination.

All of these activities seem to represent an effective beginning of activity in the area of research results dissemination.

Summary

Thus, it is clear that the mission of the NIH is being considerably broadened with the growing activity in demonstration and control programs, clinical trials, and information dissemination. There is considerable anxiety at NIH about the dilution of basic research efforts. Thus far, there is no evidence that the basic research enterprise has suffered; however, it is certainly conceivable that it could be damaged with further expansion of the NIH role without additional personnel and financial resources.

CHAPTER 5

The Intramural Research Program of the National Institutes of Health

As noted in Chapter 3, the conduct of biomedical research within the walls of NIH is the oldest of the missions of NIH. Ten of the eleven institutes have intramural programs, the National Institute of General Medical Sciences being the only exception.

The intramural program is generally considered to be of very high caliber enjoying both a national and an international reputation. Some would consider it to be the best general medical research institution in the world. To quote Dr. Arthur Kornberg,[43] Professor of Biochemistry of the Standord University School of Medicine and a Nobel Prize winner, "As for research achievements in the last 25 years, no single institution has so dominated the journals of basic medical science, and some of these contributions have been of stellar magnitude."

Yet, the intramural program has come under indirect attack—several present Administration officials stated that they feel all research should be done by outside institutions—and some feel it is beginning to show signs of notable deterioration. There seems to be a serious morale problem throughout NIH. This has been alleviated recently by the appointment of a new Director of NIH who seems to be universally acclaimed as precisely the type of Director needed.

The question often arises, why have an intramural research program at the NIH? This question has been consistently raised during the last several years, both by Administration officials in private and by outside researchers who have long maintained that NIH intramural research is not subject to the same critical review and competition for support as is the case with the grant process. Some would answer merely because it is there. A large investment has been devoted to building up the physical plant, the equipment, the personnel, and so forth, and it makes little sense to destroy that resource upon which important new tasks may devolve. However, there is a number of more specific and obvious reasons for preserving an intramural program at NIH:

1. There is evidence that the program is well-managed and of high quality. Not only has the program produced good research, but many observers feel that it has been more productive than alternative resources such as medical schools which have had equivalent amounts of money.
2. Most NIH staff feel deeply that the intramural program is necessary to preserve a unique ambience at NIH. The existence of an extraordinarily well-equipped center staffed by a concentration of highly-qualified professionals has indeed been a magnet

[43] Kornberg, A., Statement Before the Subcommittee on Public Health and Environment, Interstate and Foreign Commerce Committee, House of Representatives, April 21, 1975.

for attracting the most excellent scientists for short-term collaboration in the peer review system, the national advisory councils, and so forth.

3. The NIH pioneered in ways of conducting basic research which have become accepted elsewhere and are emulated even today. M.D.s and Ph. D.s work side by side and readily consult those of other disciplines in a way which is not always true of medical school researchers. The model of basic research associated with the Clinical Center set a pattern which has been followed all over the world.

4. An often overlooked value of the intramural program is that it is a training ground for scientists and science administrators. A critical need in the biomedical research enterprise is administrators who can deal not only with the financial and organizational questions of grants and contracts, but have scientific familiarity with the issues. Most of the scientific administrative personnel at NIH are products of NIH, and there are also many in other institutions who have become deans, chairmen of departments, and so forth, who are "graduates" of the NIH intramural program.

5. The direct training function of the Research Associate and Clinical Associate Programs have certainly been important for young scientists.

6. Certain types of research can be done under tight controls in the intramural program, and if they are promising can then be developed for expansion under contract. The therapeutic successes in Hodgkin's Disease were developed in this way.

7. Finally, the NIH is of considerable importance in international diplomacy in biomedical science. An endless stream of visitors and researchers in residence from other countries pours through. At any one time, there is a large number of scientists from other countries working at NIH. Medical science can sometimes even open channels of communication which traditional diplomacy is not able to open.

8. Some types of work can be done at NIH which are difficult to do elsewhere. For example, large clinical trials can be organized and coordinated centrally. Unpopular causes, such as testing frauds, can perhaps be done more easily in such a setting.

The counter-question is why should there not be an intramural program? What intrinsically precludes government from conducting research itself? This question has no good answer. There are those in the Administration and the outside research community who are ideologically opposed to having the government directly involved in medical research; in addition, many outside institutions seem to criticize the support which now goes to the intramural program simply because they would like to receive it. These are not adequate reasons for destroying that program.

The total cost of the intramural program in 1974 was $186.7 million, or 10.5% of the total NIH appropriation. Table 8 shows the percentage of research funds invested by each institute in the intramural program. It is interesting to note that that percentage varies from a low of 7.6% to a high of 29.3%. One assumes that a critical mass of researchers is necessary for a successful intramural program

and that that critical mass takes a larger percentage of a small institute's resources. The intramural programs occupy approximately 1,300,000 square feet of laboratory and office space, not including the clinical areas of the research hospital, the outpatient departments and attached service area shops, animal supply areas, library and so forth. Most of the space is on the Bethesda campus, but some overflows into rented space in the vicinity. The intramural program of the National Institute of Environmental Health Sciences is located in North Carolina. Research activities are also found in the animal center in Poolesville, Md., at Ft. Detrick (National Cancer Institute, National Institute of Neurological and Communicative Disorders and Stroke), at the Rocky Mountain laboratory (National Institute of Allergy and Infectious Diseases), and Phoenix (National Institute of Arthritis and Metabolic and Digestive Diseases).

TABLE 8.—*Intramural research effort by Institute, 1974*

Institute and percent of total research funds for intramural research:	
NCI	[1] 8.9
NHLI	7.6
NIDR	16.4
NIAMDD	14.7
NINDS	16.4
NIAID	19.2
NIGMS	
NICHD	11.5
NEI	
NIEHS	29.3
NINDS and NEI	

[1] NCI figure is for 1976.

Source: "Health Program Memorandum and Discussion of Budget/Legislative Issues, 1976–1980," Assistant Secretary for Planning and Evaluation, Department of Health, Education, and Welfare, July, 1974.

The intramural program is apparently a very attractive place for a scientist to work, aside from the problems of salary and personnel positions which will be described further later. Some of the reasons for this include:

1. The relative freedom from administrative and teaching responsibilities which permits almost fulltime devotion to scientific research.
2. The excellent resources in terms of equipment, animals, patients, and so forth.
3. A high degree of assurance of continuous support, allowing opportunity for long-term experiments.
4. The extraordinary opportunities for multi-disciplinary collaboration and consultation.
5. The high degree of freedom given to independent investigators in the selection of research programs and the direction of their own activities.

While these reasons imply an extraordinary degree of protection and freedom to intramural investigators, in an age when accountability is being stressed, the accountability of the intramural scientist is indeed lacking. The focus of review procedures is on the individual, particularly with regard to his being granted tenure and being promoted. There is no question that this function is carried out in a highly critical and professional manner. However, it seems apparent that the research itself is seldom reviewed in a manner and with a

frequency such as that applied to individual research grants made to outside investigators. An intramural scientist merely needs the approval of his branch or lab chief to embark upon a scientific project that can be pursued within the limits of available resources.

The vast majority of scientists at NIH are in the career service, and as such have full tenure. Cases of removal for poor productivity or lack of scientific excellence are a rarity. The problem of excellence and productivity is particularly acute with respect to aging scientists. With the end of the NIH growth period, the entire staff is gradually aging, and eventually there will be serious problems of productivity because new blood has not been brought in and nurtured. All informants reported that scientific research is basically done by young scientists. Several institute directors were quite candid about identifying laboratories in their institutes which could probably be phased out to make room for younger, more productive scientists. However, only one laboratory has been closed, and that has raised serious problems of how to deal with the involved scientists who are tenured under Civil Service. One institute director went so far as to say that this is in his opinion the most serious problem facing NIH at the present time.

It seems appropriate that the NIH leadership address itself actively to the problem of the unproductive scientist. Two suggestions were frequently made in the interviews: (1) more active attempts could be made to train such scientists in science administration, and (2) such scientists could be transferred to regulatory agencies such as the Food and Drug Administration or the Environmental Protection Agency which are said to have a great need for competent scientists with management abilities.

Another problem facing the intramural program is that of the ceiling on personnel positions. The overall personnel positions problem will be discussed in Chapter 9. At this point, only the numbers of personnel positions in the intramural program will be presented. Table 9 shows the permanent personnel in the intramural research program by Institute, beginning in 1968. One can readily see that only three institutes gained intramural personnel during that period of time, the National Cancer Institute, the National Institute of Environmental Health Sciences, and the National Institute of Child Health and Human Development. There was in addition a new institute, the National Eye Institute, which gained. All other institutes lost intramural personnel during that time. The National Institute of Neurological and Communicative Disorders and Stroke lost approximately 30% of its entire program, which suggests a need for explanation, in view of the high interest in Congress in such disorders. The National Heart and Lung Institute lost approximately 6% of its intramural program during a time of heightened concern about heart disease and establishment of new programs in lung diseases and blood diseases.

Under the pressures to expand its mission, the personnel situation has certainly produced inefficiencies and counterproductive attempts to economize. Several situations were pointed out where it appeared that the absence of positions cost the government more than the cost of the needed staff, and has reduced quality of the work as well. Of course, NIH could be faulted in some of these cases for not cancelling programs of low priority. But in general, the restrictive personnel policy has caused great problems.

TABLE 9.—FULL-TIME PERMANENT PERSONNEL, 1968–75, NIH INTRAMURAL PROGRAM

	Total	NCI	NHLI	NIDR	NIAMDD	NINDS	NIAID	NIGMS	NICHD	NIE	NIA	NIEHS
1968	4,053	1,229	444	235	526	582	626	----------	292	----------	----------	119
1969	3,921	1,192	405	225	517	566	620	----------	269	----------	----------	127
1970	3,810	1,143	404	216	494	465	603	----------	280	52	----------	153
1971	3,862	1,205	411	213	501	460	592	----------	248	55	----------	177
1972	4,089	1,419	424	214	487	447	551	----------	282	76	----------	189
1973	4,113	1,443	417	215	491	419	535	----------	330	79	----------	184
1974	4,152	1,481	424	197	476	425	525	----------	347	87	----------	190
1975	4,129	1,492	420	192	473	413	516	----------	342	89	----------	192

Note: NCI—National Cancer Institute; NHLI—National Heart and Lung Institute; NIDR—National Institute of Dental Research; NIAMDD—National Institute of Arthritis, Metabolism, and Digestive Diseases; NINDS—National Institute of Neurological and Communicative Disorders and Stroke; NIAID—National Institute of Allergy and Infectious Diseases; NIGMS—National Institute of General Medical Sciences; NICHD—National Institute of Child Health and Human Development; NEI—National Eye Institute; NIA—National Institute on Aging; NIEHS—National Institute of Environmental Health Sciences.

Role of the Intramural Program

The question often arises as to how the intramural program should be using its resources. All institute directors were asked for their views on this matter. There was considerable difference of opinion, with several directors of the view that the intramural program should do essentially what is done outside the NIH, and with others feeling that the intramural program should take essentially a complementary role. Probably because of this difference of opinion, the role of the different intramural programs tends to vary somewhat. However, there are many activities presently going on which are complementary to the outside world in the sense that they are too expensive, too risky, too uncertain or have too long a time frame. There are also research activities underway in areas where there is a definite national lack of research resources.

For example, the National Cancer Instutute has an effort underway of potentially nationwide importance to automate cytology testing. This offers the potential of improving cytologic screening, with earlier cancer detection the goal. The equipment is expensive, the work tedious and time-consuming, and the payoff uncertain. The project seems unlikely to have been started in another setting.

Another type of example is the multiple risk factor intervention trial (Mr. Fit) in the National Heart, Lung, and Blood Institute, which is designed to study whether the reduction of serum cholesterol, reduction of elevated blood pressure, and elimination or reduction of cigarette smoking will produce a significant reduction in morbidity and mortality from coronary heart disease. This trial resulted in total obligations of $12,590,000 in fiscal year 1975, and involves thousands of people.

A final example is in parasitic disease work in the National Institute of Allergy and Infectious Diseases. Although parasites do still cause some disease in the United States, in general this is a problem of developing countries. Because of the small number of parasitologists in the world, the National Institute of Allergy and Infectious Diseases has maintained a parasitic diseases research section which is carrying out studies ranging from laboratory to field epidemiology.

These examples illustrate that NIH has been sensitive to priorities in its intramural program. But it is critically important that NIH have the flexible resources in this program to support long-term research, large clinical trials, or research on unpopular topics.

The Clinical Center

In the mid-1940's, recognition of the need for coordination of basic clinical research on long-term illness resulted in recommendations for the establishment of the Clinical Center. In 1947, construction funds were appropriated for the facility which would house a hospital and nearby laboratories, so that all stages of selected chronic diseases could be intensively studied. A minimal out-patient department was designed to permit following patients after hospitalization. During the mid-1950's the average length of hospitalization exceeded 40 days and out-patient visits were rare. By 1960, inpatient length of stay was declining, and by 1970 had fallen to 28 days. At the same time, outpatient visits had been increasing to 17,000 in 1960 and

47,000 in 1970. Outpatient visits are projected to about 75,000 in fiscal year 1975.

At the time it was built, many of the design features incorporated in the Clinical Center represented definite innovations, as mentioned earlier. Many other institutions have followed the same model, which has helped basic research remain connected to clinical application. The Clinical Center has proven to be extremely important to the work of an institution such as NIH.

One particular problem with the operation of the Clinical Center has been the allocation of beds. An allocation was made shortly after the Clinical Center opened in 1953, and has been only slightly changed since. A problem of mismatch between needs and allocation was mentioned several times by NIH staff, which cited an overall utilization rate of only 62%. The utilization rate by institute is shown in Table 10, and varies from virtually zero to the high 80's. The Cancer Institute uses its beds so actively that it has had to contract with two outside facilities at a time when 38% of the Clinical Center beds were going unused. Those involved in the administration of the Clinical Center, both past and present, readily admit that the present allocation is in need of review, and probably in need of alteration as well. However, they also identify the subject as an extremely sensitive internal political issue, which has been carefully avoided. A critical assessment is now underway. The NIH sent out a Request for Proposal for a contract on April 4, 1975 for a study of constraints on bed utilization at the Clinical Center. The report should be available shortly.

Parenthetically, it should be noted that a research institution such as the Clinical Center would not be expected to run at 100% occupancy. Seasonal changes, attendance at the Spring scientific meetings, and needs for isolation of certain patients all cut down on average utilization. Clinical Center staff estimate that 80% is a reasonable reflection of full utilization of the facility.

The Ambulatory Care Research Facility

The need for ambulatory services seems clear in the statistics quoted in the previous section. The NIH projects a cumulative demand for 194,000 annual ambulatory patient visits by the year 1980. This results from a gradual reorientation of biomedical research. Early research at the Clinical Center was primarily concerned with the understanding of long-term illness, and required prolonged periods of hospitalization under highly controlled conditions. Over time, however, increasing effort has been directed towards the understanding of the biological mechanisms underlying disease. Early detection is emphasized, together with the testing of diagnostic and therapeutic modalities after disease onset. As a result, clinical research now frequently employs large clinical trials involving patients who can carry on a normal life while being treated and evaluated for research purposes in the outpatient setting. In these circumstances, hospitalization can be expected to be episodic rather than prolonged.

An ambulatory care research facility has been proposed that would add 212,000 net square feet of space to the approximately 1,187,000 net square feet of space at the Clinical Center. One-half of the new space will be devoted to clinics and associated research laboratories

and offices. The remaining new space will be equally divided between relocated activities and new support functions. The relocated activities include diagnostic radiology, surgery, and radiation therapy. The facility has been designed, but has been delayed by the Department of HEW for several years. An approval to proceed with construction is anticipated shortly by NIH officials. This construction seems warranted for a number of reasons, the most important of which are as follows:

TABLE 10.—UTILIZATION OF THE CLINICAL CENTER, NIH CENSUS ANALYSIS, INPATIENTS, PERIOD COVERED MAY 1, 1974 TO APRIL 30, 1975

Institute	Total beds	Average daily census	Percent bed occupancy
NCI	118	77	65
NHLI	102	53	52
NIAID	52	38	73
NIAMD	64	38	59
NIDR	5	1	12
NIMH*	74	43	59
NINDS	50	37	73
NEI	26	15	60
NICHD	20	15	73
Total	511	316	62

*National Institute of Mental Health.

1. There is a great deal of evidence of obsolescence and crowding in the present facilities. For example, animals are housed in close proximity to patient care areas. Patients are treated in areas which are not intended to be patient care areas. Equipment is stored and sometimes used in hallways. Renovation is a critical need.

2. Perhaps even more important is NIH's expanded role into ambulatory clinical research and epidemiological research. Already other research institutions are ahead of NIH in the area of ambulatory clinical research. A fruitful future for biomedical research will require interaction of three dimensions, the basic science dimension, the clinical perspective, and the population or epidemiological perspective. The ambulatory clinical center offers the opportunity to bring a population dimension to the intramural program at NIH.

Summary

The NIH intramural program has been exceedingly productive and is world-recognized for its excellence. On the other hand, it is not without serious problems bearing on its future effectiveness unless prompt and insightful action is taken by NIH management. There seem to be overwhelming arguments for the strengthening of this program. Specific problems requiring action are pointed out in this Chapter.

CHAPTER 6

Extramural Research Programs of the National Institutes of Health

Extramural research programs constitute the largest part of NIH activities. Table 11 shows obligations by funding mechanism for fiscal year 1974 for institutes and research division. Of the total obligations of almost $2 billion, $765 million was committed to regular grants, $335 million to research and development contracts, and $246 to research centers and research resources grants. These three categories alone make up more than half of the NIH budget, most of the balance going primarily to the intramural program and to research training.

RESEARCH GRANTS

As noted, regular research grants make up the largest category of NIH expenditures. The most common purpose of these grants is to stimulate research in medical and other health related fields, and the most common approach used is to provide funds for the support of particular projects initiated and proposed by individual scientific investigators. Although defended by individuals, grants are actually made to universities, medical schools, hospitals, and other public and private non-profit institutions and agencies where the investigators are employed. Research grants may be used to pay the salaries of personnel, for the purchase of equipment and supplies, and for travel, publication, the institutions' direct costs, and other purposes directly associable with the research. The award also includes an important component of reimbursement to the investigator's institution to cover indirect costs, or overhead.

TABLE 11.—ACTUAL OBLIGATIONS BY FUNDING MECHANISM, FISCAL YEAR 1974: INSTITUTES AND RESEARCH DIVISIONS[1]

[In thousands of dollars]

Mechanism	Total	NIAID	NIAMDD	NCI	NICHD	NIDR	NEI	NIEHS	FIC	NIGMS	NHLI	NINDS	DRR
Total	$1,945,224	$120,822	$177,374	$581,021	$144,146	$50,020	$45,155	$32,126	$5,048	$188,600	$327,250	$143,535	$130,127
Research programs	1,614,357	108,025	153,584	463,598	121,935	38,284	37,646	26,093	2,894	121,226	293,104	120,848	127,120
Regular grants	765,121	64,853	114,300	114,507	75,431	17,063	29,092	11,541		89,517	170,425	78,392	
General research support grants	78,746	3,819	6,179	776	2,950	780	1,170	372		5,299	1,067	4,137	52,197
Centers, resources and other grants	24,166	4,562	3,349	104,132	7,765	7,895	643	4,044	500	23,970	9,128	7,514	72,664
Animal centers	17,793												17,793
Biotechnology resources	12,551												12,551
General clinical research centers	42,320												42,320
Research career award programs	23,532	2,202	3,349	1,673	2,157	403	643	159		7,092	4,231	1,623	
Specialized research centers	98,685			92,452		342						5,891	
Other special grants	51,285	2,360		10,007	5,608	7,150		3,885	500	16,878	4,897		
Laboratories and clinics	134,122	20,733	20,848	23,267	14,068	7,630	4,245	8,369			21,585	13,377	
Research and development contract	335,291	12,293	7,002	180,360	21,132	3,745	2,099	1,767		2,440	90,899	11,295	2,259
Collaborative research and support	50,383	1,765	758	40,556		1,171						6,133	
Biometry, epid. and field studies	2,134		1,148		589		397						
International center	2,394								2,394				
Research training	186,489	9,237	18,988	23,562	14,824	8,895	5,773	4,594	2,154	59,721	19,395	18,712	634
Grants	153,573	7,452	15,013	17,558	12,607	7,193	3,857	4,038		53,617	16,933	14,868	437
Fellowships	32,916	1,785	3,975	6,004	2,217	1,702	1,916	556	2,154	6,104	2,462	3,844	197
Construction programs	38,090			38,090									
Cancer control programs	33,758			33,758									
Program management[2]	72,530	3,560	4,802	22,013	7,387	2,841	1,736	1,439		7,653	14,751	3,975	2,373

[1] Includes $219,082,000 in fiscal year 1973 released funds. [2] Includes scientific evaluation grants.

Source: National Institutes of Health, "Basic Data Relating to the National Institutes of Health, 1975."

Much of the responsibility for administering the grant program is centered in the Division of Research Grants (DRG), although each institute participates in the process to a material extent with regard to grants awarded out of its individual appropriation. The Division collects, stores, analyzes, evaluates, and retrieves management and program data needed in the administration of these programs. Advisory and consultative services relative to grant policy and management matters are provided to the grantees. The Division also administers the Grants Associates Program for the training of science administrators.

Finally, but very importantly, the Division screens all incoming grant applications and makes assignments to the various NIH institutes, as well as to other components of the Public Health Service. DRG further assigns NIH grant applications to the DRG-administered initial review groups (Study Sections) for scientific review and to institutes or other awarding units for possible funding. The assignment is not made arbitrarily but in response to referral guidelines articulated by each institute or agency expressing its specific areas of research interest:

As indicated, the initial scientific review is carried out by forty-seven* regular study sections made up of outside scientists and administered by DRG. The study sections systematically cover the various specialties in the fields of science. Congress was recently advised by a noted scientist that, "The system of research grant applications by investigators whose proposals would be evaluated by their scientific peers was designed to evoke the creative talents and energies of the nation's scientific community. The peer review system has on the whole worked and worked well."[44] Most persons within and outside of the biomedical research community agree that, *on balance*, the peer review system has been an effective mechanism.

The peer review system is consonant with the nature of basic research. Dr. Lewis Thomas has described this succinctly:[45] "This is the element that distinguishes applied science from basic. Surprise is what makes the difference . . . what you need at the outset is a high degree of uncertainty; otherwise it isn't likely to be an important problem. You start with an incomplete roster of facts characterized by their ambiguity. Often the problem consists of discovering the connections between unrelated pieces of information. You must plan experiments on the basis of probability, even bare possibility, rather than uncertainty. If an experiment turns out precisely as predicted, this can be very nice. But it is only a great event if at the same time it is a surprise. You can measure the quality of the work by the intensity of the astonishment."

Each of the study sections is made up of 10 to 15 highly qualified nongovernment consultants selected on the basis of their recognized competence and achievements in their respective research fields, who serve terms of up to 4 years. Each section has an Executive

*Four study sections were added on 4/25/75 and two others in 1975. These have not been included in this analysis.

[44] London, I. M., Testimony Before the House Subcommittee on Public Health and the Environment, Interstate and Foreign Commerce Committee, April 21, 1975.

[45] Thomas, L., *The Lives of a Cell*, New York, Viking Press, 1974, Pages 118-119.

Secretary who is a Health Scientist Administrator on the professional staff of the Division of Research Grants. The Executive Secretary reads each application and assigns it to two or more members of the study section he considers best qualified to judge the application in detail. An analysis for the June 1974 to March 1975 review cycle showed that the sections reviewed from 40 to 368 grant applications each, for a total of 10,658 applications.

Sometimes DRG will be receptive to applicants as to what study section the application should go to since a certain section or member may be already familiar with the subject area or the work itself. The members receive the applications six to eight weeks before the section meetings, which are held three times a year, and they are expected to give a detailed report on that application in addition to reading all of the other applications that will be reviewed at the meeting. These reviewers can seek outside assistance if necessary. At the meeting the application is discussed and a final recommendation is voted by the study section for approval, disapproval or deferral. For each approved application, each member privately records his or her numerical score based on his or her opinion of scientific merit relative to the state of the art. These scores are then combined into one priority score. Both the scores and the Executive Secretary's summary review of the consideration (recorded on pink and various other paper—having considerable individual significance) are considered to be proprietary information, not subject to review under the Freedom of Information Act.

At the time of the initial assessment of a proposal by the Division of Research Grants, the application is also assigned to one of more grant awarding units, usually an institute. In fact, institutes file with DRG specific instruction regarding which applications to assign them.

Each of the awarding units has a national advisory council or an equivalent unit that reviews and recommends approval of grant applications before a grant can be awarded. They include:

National Advisory Council on the Aging.
National Advisory Allergy and Infectious Diseases Council.
National Arthritis, Metabolism, and Digestive Diseases Advisory Council.
National Advisory Child Health and Human Development Council.
National Advisory Dental Research Council.
National Advisory Environmental Health Sciences Council
National Advisory Eye Council.
National Advisory General Medical Sciences Council.
National Heart, Lung, and Blood Advisory Council.
National Advisory Neurological and Communicative Disorders and Stroke Council.
National Cancer Advisory Board.
National Advisory Research Resources Council.
National Library of Medicine Board of Regents (which also serves as the National Medical Libraries Assistance Advisory Board).

The councils, established by statute, are made up of individuals who are either "authorities in scientific and health fields directly related to the program interests of the Institute or lay people noted for their interest or activity in national health problems." Members,

except for the National Cancer Advisory Board and NLM Board of Regents, are selected by the Secretary of the Department of Health, Education, and Welfare, after receiving the nominations from the particular institutes, and serve four year terms. The Cancer Board is Presidentially appointed and the Board of Regents is submitted by the President for the consent of the Senate. The councils meet three times a year about six to eight weeks after the study section meetings.

The councils receive the study section recommendations on grant applications and review the proposals against a broad background of responsibilities that include, in part, a determination of the needs of the NIH, the degree of relevance of the proposed research to the mission of the institute, the need for initiating research in new areas, and other policy matters. The priority scores assigned to the grant applications by the study sections serve as a virtually inviolable guide to the national advisory councils and to the awarding units in their decisions regarding the order in which the approved grant applications will be funded. While the councils cannot change the priority scores set by the study sections, they can recommend that an approved application be classified to be funded or not to be funded. This classification is to be based on high or low program relevance and not on the proposal's scientific merit. The fact that a grant application has been approved by the national advisory council is no guarantee that an award will be made since there may be more approved applications than funds available, but if the council disapproves an application, it cannot be funded.[46]

Criticism of the Study Sections

The peer review system has come under some attack in recent years, particularly by the Office of Management and Budget.[47] Such problems as conflict of interest, concentrating research funds on a few select institutions, the lack of administrative direction of the allocation of research funds, and the subjective nature of the assessment have all been cited as problems. In addition, the process is criticized for being reactive to the initiative, interests, and whims of individual researchers and therefore not readily compatible with targeted or directed research.

The most noteworthy concerns are described as follows:

1. The system deters the support of applied research having a more obvious prospect of relatedness to disease problems. The system has a strong bias for basic scientific inquiry and a disdain for applied research. This, coupled with *managerial choice* to strictly follow descending project priority in funding individual investigator grants tends to assure that applied work or work of greater program interest to the institutes does not get funded.
2. The selection of study group members has been criticized as a fraternity wherein:
   (*a*) only a certain "in-group" is chosen or used as a source of nominations for appointment. Some scientists have charged that they were "blackballed."

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[46] This process is well described in G. N. Eaves, "Who Reads Your Project-Grant Application to the National Institutes of Health," *Fed. Proc.* 31: 2–9, January–February, 1972.

[47] Office of Management and Budget, "The National Institutes of Health and National Institute of Mental Health Peer Review System," March, 1973.

(5) it has been alleged that awards are unexplainably frequent to either study section members or their colleagues.

3. The review process is covert, conducted in an atmosphere of secrecy, with findings closely guarded from public release. Quite recently this situation led to a court suit in which NIH was held in violation of the Freedom of Information Act for not agreeing to release information regarding funded research grant applications (Washington Research Project Inc. versus Secretary DHEW). This case is on appeal.

4. The makeup of the study sections has been criticized on the basis of the geographic spread of the investigators represented, institutions represented by the investigators, age of the investigators, and so forth. A simple analysis was carried out to determine the geographic and institutional distribution of the investigators, which showed a wide spread in both parameters. On the other hand, there are few young scientists on the present study sections. Only 2.9% of all members were under 36 years of age, 17.8% were 36–40, 29.0% were 41–45, 28.9% were 46–50, 13.6% were 51–55, 4.6% were 56–60, and 2.8% were over sixty. The rest were not classified by age.

A section-by-section analysis showed that 28 of the 47 sections had no representation under 36 years of age. Eighteen sections had only one member, and one section has two members in that age category. The schedule below gives the number of study section with membership in each age category, by the number of people in each age category.

NUMBER OF STUDY SECTIONS WITH REPRESENTATION[1] IN VARIOUS AGE CATEGORIES[2]

	Under 36	36 to 40	41 to 45	46 to 50	51 to 55	56 to 60	Over 60
Number of members in age category:							
0	28	4		1	9	28	33
1	18	8	1	4	15	11	11
2	1	13	7	7	7	6	2
3		8	12	6	7	1	
4		7	8	6	2	1	1
5		6	7	11	7		
6		1	6	7			
7			4	1			
8			1	2			
9			1	2			
Total	47	47	47	47	47	47	47

[1] Member listings as of Mar. 14, 1975.
[2] Ages as of June 30, 1975.

Source: Data supplied by the Division of Research Grants.

This is a serious matter since it is often asserted that science belongs to the young and it is certainly known that science has its own orthodoxy.

In conclusion, although subject to some questions regarding objectivity and practice in accord with contemporary standards of public agency behavior, the NIH peer review system appears to be of high quality and worth *preserving* and *strengthening*.

The National Advisory Councils

The situation with the national advisory councils was judged to be considerably more distressing. These advisory councils have a potentially very important role in determining relevance of specific projects and also in helping to determine the thrust of a particular institute's program. This important task obviously requires a great deal of wisdom and insight as well as technical knowledge. In addition to these general characteristics, recent developments have lead to attempts to give minority groups, young people, and women some representation on the national advisory councils. The general opinion about this at NIH is that it still allows selection of a competent and active advisory council. However, during the past several years, partisan politics have become actively involved in the selection of the members of these councils. It is recognized that the Administration has always interferred to a limited extent in such appointments, but this interference has seemed to reach alarming proportions during the last few years. A question of caution, however, is in order as to whether such interference is continuing as actively as previously, and whether NIH staff is reflecting memories of the recent past or continuing interference.

Furthermore, the delays presumably attributable to the political review in DHEW and in the White House of suggested names are perhaps *more serious* than partisan political factors. It is typical now for an institute director to submit three names for his national advisory council and six months to a year later have one, two, or all of them rejected. This has reached a point where some national advisory councils have had insufficient membership to form a quorum. Table 12 provides an overall view of the number of vacancies as of January 1, 1975, and also the years from which the vacancies date. The Table does not include the National Cancer Advisory Board since appointments to it, as noted earlier, are made by the President on the basis of nominations received from a number of sources. The National Cancer Institute sends its nominees directly to the President, without their having to go through the NIH and HEW review process. The National Library of Medicine's Board of Regents are nominated by the President and must be confirmed by the Senate, but NIH does make suggestions for these positions which go through the regular HEW channels. Therefore, they have been included. As can be seen in the Table, 12 of the 62 vacancies, or about 20%, were over a year old. It is the universal consensus of NIH institute directors, all of whom were interviewed, that the amount of time to get positions filled is often excessive.

The backlog of vacancies in the national advisory councils decreased considerably in the first half of calendar year 1975, making the situation a little less critical, but nevertheless important. As of July 24, 1975, there were 43 vacancies to be filled in the councils listed. This includes seven for the National Library of Medicine, which is authorized ten members. This is an inadequate number to constitute a quorum and certainly not a sufficient number to review all of the National Library of Medicine grants and contracts which account for half of the National Library of Medicine budget. While the number of vacancies has decreased, it is still too early to tell if the overall approval times have changed significantly, since many of the 1975 slates were still pending in July, 1975.

Related to the time factor is the success rate of NIH submissions to HEW. Table 13 analyzes the appointments of professional members to councils, and shows the success rate of the NIH nominees for council professional positions. The appointments of the lay members have been excluded; the situation with the latter appointments will be discussed later. As can be seen in the Table, it has been since about 1970 that the non-NIH candidates have been selected for positions on the councils. The number of vacancies also began to rise about 1970.

TABLE 12.—ANALYSIS OF APPOINTMENTS OF MEMBERS OF THE NATIONAL ADVISORY COUNCILS AS OF JAN. 1, 1975

Council	Authorized positions	Actual members	Vacant positions	Year positions become vacant		
				1972	1973	1974
Aging	12	0	12			12
Allergy	15	7	8	1	1	6
Arthritis	18	12	6		1	5
Child health	14	9	5		2	3
Dental research	12	7	5	1		4
Environmental health	12	11	1			1
Eye	12	8	4	1		3
General Medical Science	12	8	4			4
Heart and lung	18	14	[1] 4			4
Neurology and stroke	12	9	3			3
Research resources	12	6	[2] 6	1	2	3
National Library of Medicine	10	6	4	1	1	2
Total	159	97	62	5	7	50

[1] 3 appointments were made in January 1975.
[2] 6 appointments were made in January 1975.

Source: NIH Committee Management Office memo dated Jan. 30, 1975.

TABLE 13.—ANALYSIS OF APPOINTMENTS OF PROFESSIONAL MEMBERS OF NIH NATIONAL ADVISORY COUNCILS SUMMARY AS OF JAN. 1, 1975

	1965	1966	1967	1968 [2]	1969	1970	1971	1972	1973	1974
Vacancies	16	22	16	24	34	29	30	34	37	41
NIH candidates [3]	34	43	33	52	72	53	40	70	54	88
NIH candidates approved [4]	20	21	18	25	34	25	17	16	14	10
Other candidates [5]	1	0	0	0	1	5	8	5	5	9
Invited [6]	21	21	18	25	35	30	25	18	19	16
Declined	5	3	2	1	3	4	1	1	1	3
NIH candidates appointed	15	18	16	24	32	23	16	15	14	8
Other candidates appointed	1	0	0	0	0	3	8	2	4	3
Remaining vacancies	0	0	0	0	2	2	6	17	19	30
Authorized professional positions	64	64	64	80	88	91	95	95	97	99
Total authorized positions	96	96	96	118	130	134	141	142	144	147

[1] Excludes the National Cancer Advisory Board.
[2] The National Library of Medicine was transferred from the Public Health Service to the National Institutes of Health on Apr. 1, 1968.
[3] The number shown as "NIH candidates" is the number that have passed an initial HEW screening process (for present service, etc.). These may include some names that were recommended by HEW to NIH, but NIH has concurred in them.
[4] Approved means the final approval by HEW but does not necessarily mean invited.
[5] Other candidates are those initiated by other than NIH and that NIH has not concurred.
[6] Not all of those approved are invited.

The amount of time involved from NIH submission to HEW appointment seems excessive and is the cause of a number of vacancies. Further, a serious question exists regarding whether council members should be politically cleared before appointment. In this regard, some have suggested that the selection process should be the responsibility of NIH, not the Department of HEW, and that NIH be held accountable for the success of the councils.

According to NIH guidelines, "within a given Council, representation of needed or scientific disciplines . . . must permit attainment and maintenance of a proper balance to cover the range of the mission and goals of the Institute." [48] It seems reasonable that NIH have primary responsibility for selecting these individuals, in accord with clear guidelines.

According to NIH guidelines, lay members who are selected for national advisory councils are public representatives with a demonstrated interest in the workings of the institute. They should have knowledge concerning the needs and aspirations of society in the areas of the missions of the institutes. A large number of persons appointed to these lay positions are HEW selections. NIH's success rate for lay position approval is not as high as that for professional positions. The institutes have also noted that lay members are not always familiar with the institute and its subject area. This creates a problem in assigning grant applications for review, since the member is not familiar with a particular area. Public members have a vital function to fill, and their selection should be as important and as careful as the selection of the scientific members.

Parenthetically, it might be noted that the White House has denied its involvement and has stated that the political affiliation of potential candidates in no way prejudices their appointment to HEW advisory councils. This statement is extremely hard to accept in the presence of both narrative and statistical evidence to the contrary.

Another apparent problem with advisory councils is that certain disciplines which could be useful in assessing relevance, such as law and sociology, are hardly represented on the councils. More attention to the selection of public members in this regard might be beneficial.

To be effective, a lay member of a council must have some degree of knowledge in the area of biomedical research. Several informants have suggested some type of formal orientation or course for such members. Several institutes already provide some opportunities for council members to become more knowledgeable in the workings of their institutes and program areas, enabling them to make better decisions in determining program relevance of grant proposals. Some of these activities are listed below:

In the National Institute of General Medical Sciences, Council members meet with the Institute's program personnel and prepare an annual report on the programs to the Institute.

In the National Institute of Child Health and Human Development, each of the program areas of the Institute reports to the Council at its regular meetings, along with presentations from an intramural scientist and a person from outside the Institute. The Council can also request the Institute to prepare special reports in areas in which they are interested. Also, Council members are welcome at any of the Institute's review committee meetings or at Institute-sponsored scientific meetings. In 1974, about half of the Council members attended at least one of these conferences or meetings. They may also make site visits with institute personnel.

In the National Institute of Arthritis, Metabolism, and Digestive Diseases, the Council members spend the day before the

[48] NIH Committee Management Office memo, dated Jan: 30, 1975.

regularly scheduled meeting in sessions with institute personnel in their program areas.

The National Advisory Eye Council recommended establishment of a Vision Research Program Planning Committee. The Committee was charged with conducting an extensive analysis of the Institute's current research program and generating recommendations to the Council concerning future support of vision research. The report was prepared with the assistance of the Institute staff and leading investigators in each major field of vision research.

In the Heart, Lung, and Blood Institute, National Advisory Council members have a standing invitation to attend any of the Institute's advisory committee hearings, but this is seldom taken advantage of by the members. Members are kept up to date in program areas via presentations by the Institute staff at the National Advisory Council meetings. The Council also produces, as required under the Heart Act, an annual report on the status of the Institue's programs as it sees them.

In the National Institute of Allergy and Infectious Diseases, there is a half day orientation program for new Council members to get introduced to the program areas and staff. Each segment of the Institute, on a rotation basis, makes a presentation at the regular NAC meeting. Also, members are welcome to accompany Institute personnel on site visits.

In the National Cancer Institute, one of the four meetings of the Council in a year is devoted solely to program review—no grants are looked at. Presentations are made on the status of the NCI programs both internally and on a national basis. Outside speakers are included. The Council is also divided into subcommittees, one of which is the Subcommittee on Cancer Centers. It arranged a meeting in September 1975 to look at the initial review criteria used, improvements in coordinating centers' activities, etc. It has invited representatives from the Cancer Centers and from NIH extramural program.

In the National Institute of Dental Research, the new National Advisory Council members spend a day with the Director and staff where they are briefed on the intramural, extramural and collaborative programs of the Institute, its mission, its priorities and how they are set, etc. The Council members may be brought in to serve as ad hoc members of contract review committees. They may also attend Board of Scientific Counsellors meetings, and make site visits. The Institute's scientific conferences are open to Council members, though they are not specifically invited.

In the National Institute of Environmental Health Sciences, the Council members receive copies of a number of Institute publications, news releases, and summaries of intramural research projects. They are also invited to attend conferences held by the Institute and to go on site visits. Also, Council meetings are attended by the directors of the seven Environmental Health Science Centers and the members are invited to attend the Director's meetings. At the regular Council meetings, each branch makes a presentation before the Council.

In the National Institute of Neurological and Communicative Disorders and Stroke, the program area chiefs make a review of

their areas at the Council meetings. New Council members are given a one day orientation on present issues, functions of NIH and the Institute, and so forth.

The National Institute on Aging is still a relatively new institute and has not had time to develop such a pattern of activities.

The Division of Research Resources. One program area is presented at each National Advisory Council meeting. The members are kept up to date through a variety of reports prepared by the Director of the Division, Executive Officer, etc. The members may also make site visits with Division staff. Once every few years a NAC meeting is held at a site where resources are supported by the Division.

Evidence of interest on the part of the Administration in influencing appointments to advisory councils is not necessarily unhealthy, although it seems to have been carried to a new extreme. A good question is whether or not a council appointment is not of equal significance to appointment to regulatory or other governmental commissions where political loyalty is expected. Also, NIH historically has not been receptive to lay involvement in decision-making.

There is ample evidence that:

(*a*) Considerable numbers of council members do not commit themselves seriously to their participation.

(*b*) Most council actions merely "rubber stamp" staff recommendations. Few councils are willing to consider difficult issues, such as whether grant priority scores or program relevance should be the basis for awards.

(*c*) The councils often lack evidence of the type of balance of perspectives and disciplines that is needed to assure their performance.

In conclusion, the national advisory councils can play an important role in priority setting, in advising the management on program issues and in representing the view of the outside scientific and lay worlds. It seems unavoidable that politics will play some role in council selections, although for the health of the system, this must be less than has occurred over the past few years. It seems further that if the system is to work it must operate with full staffing of the councils Long delays in appointment review and processing are not compatible with this need. Finally, the management of the institutes have an important role to play in assuring effective operation of the council system. First, they must work toward getting councils that represent the type of balance of expertise and perspective needed. Second, they must assist the councils—and in fact even demand—that they work hard and focus on areas where their positions permit them to assist the nation's biomedical research program. On balance, the advisory council system works reasonably well and is essential, but, like other activities at NIH, is in need of improvement.

Grants Management

Once a grant has been awarded, the total responsibility for it transfers from the Division of Research Grants to the particular awarding unit. At this level, there is usually an Associate Director for Extramural Research whose functions include planning, policy formulation, program coordination, and the direction and administration of

the extramural program for the institute. This responsibility is further subdivided into specialized individual research grants branches. Within them, the grant administrators review grants for scientific matters, while the Grants Management and Operations Branch staff reviews the grants to be sure that all of the fiscal requirements are being met.

A number of extramural staff were interviewed to obtain their views on major problem areas. Most noted that personnel shortages have prevented optimum performance of the existing extramural staff in their duties. In order to perform with a greater degree of thoroughness and efficiency, they believe that more staff—both professional and supporting—is needed. An additional workload has also resulted from the Freedom of Information Act.

It is significant, and the Congress should be aware, that any material change in the present balance between grants and contracts in favor of contracts will demand more staff. Cancer Institute staff estimate that a Health Scientist Administrator can "administer" about 100 grants, while one scientist can "review" only about 7 contracts. This is because the investigator on a grant has almost complete freedom of action within the terms of the grant.

Another problem is that, until a firm dollar appropriation is known for the current fiscal year, the institutes do not know how much research they will be able to support. Most of those interviewed saw this as the greatest problem. It is now the practice of the institutes to assure funding to only that research that is deemed by the study sections and the national advisory councils to be the most scientifically meritorious and program relevant. All other approvals remain in abeyance until the appropriation is confirmed. With long delays in appropriation, in recent years all other grants must await confirmation of funding.

Under such a funding mechanism, many hardships and problems arise. One is that about 40% of all competing award commitments are made in May or June, and their anniversary dates for revewal will usually be fixed at the same dates. Thus the workload of extramural personnel and the councils is not equitably distributed throughout the year. Two possible solutions to this problem come to mind. The first is forward funding to enable institutes to know at the beginning of the fiscal year just what the funding level would be. This idea is appealing for management reasons, as it would allow NIH to know how many research projects could be funded during each council session. From a budgeting standpoint it would allow financial officers to obligate a realistic amount of money during the year without having to unduly tighten the awarding unit's purse strings earlier in the year. From the scientific point of view, it would allow meritorious applicant-investigators to begin their research projects without having to wait until the second half of the fiscal year, when the current appropriation is disclosed.

The second possible solution is that multiyear funding be used on a controlled basis. In this event, a research grant application might be funded for fourteen months rather than twelve. Thus the anniversary date would be automatically adjusted to a time of year when the workload is not so intense.

Another problem area is that of monitoring progress of a project. The Public Health Service Grants Policy Statement notes that "the awarding component may terminate a grant in whole or in part

any time before the date of completion if it has been determined that the grantee has failed in a material way to comply with the terms and conditions of the grant."

Some institute executive officers noted that grants can be terminated in the interest of the government, but that the mechanism apparently has not been used for terminating noncompeting continuation grants which show lack of research progress. One of the reasons for this is an attitude that seems to prevail in the institutes that there is a moral obligation to continue funding as long as funds are available. The apparent practice of dealing with less desirable ongoing research is to allow the grant to continue through its current funding period and to disapprove it when it competes again. Some noted that the time to terminate a grant under the circumstances may take longer than if the grant were allowed to expire regularly.

Final progress reports are required to be sent in within 90 days following the termination of research, but many are either late or not sent in at all. One of the reasons for this is that final publications resulting from the research usually do not appear until about one year subsequent to the termination of the project support period. The principal investigator in many instances does not submit a terminal progress report apparently because he knows that to NIH the desired result of a grant is the publication of the research findings.

The PHS Grants Policy Statement indicates that grantee failure to submit required reports may be a basis for withholding future support. Though the delinquent reports are usually pursued, very often adamantly, failure to submit a terminal report of research progress apparently does not preclude the principal investigator from receiving a research grant for another project from the same institute. The probability is even greater that it would have no effect on the funding potential from another institute, since NIH has no inter-institute policing system to detect such delinquencies.

In this area, it seems appropriate that either:

(1) The PHS policy be clarified to be either more or less demanding in terms of what is expected of investigators with regard to progress reports, or

(2) that NIH management establish and enforce policies consistent with their judgment and the PHS policy.

Overhead Charges on Research Grants

Along with items usually provided for in a research budget such as salaries, scientific equipment, laboratory and office supplies, and travel allowances, each research project benefits from and must reasonably be expected to bear the costs of the physical plant and administration of the institution at which it is conducted. These facilities and services, which include laboratory space, library facilities, light, heat, administrative and janitorial services, etc. fall into the general category of overhead.

The indirect cost allowance was limited to 8% prior to August 1955. In the early sixties, it was limited to 15%. The Federal Government went on a full cost basis in Fiscal Year 1966, but at that time the House Appropriations Committee stipulated that there should be significant cost sharing by the institution. In Fiscal Year 1967, indirect costs averaged 18.6% of direct costs, and by Fiscal Year

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1974 they had risen to an average of 31.7% of such costs. The expectation is a continual rise in indirect costs.[49]

The concern about indirect costs obviously is that the same amount of money is buying less research. This has led to increased advocacy of the earlier approach of simply placing an arbitrary limit on indirect costs. Indirect costs have obviously risen partially because of inflationary items such as fuel and utility costs. Not so obviously, new requirements placed on the institutions by Congressional and DHEW mandates contribute to the escalation of overhead. These requirements include committees to review the protection of human subjects in clinical research, more stringent requirements imposed for the care of research animals, the additional standards required by the Occupational Safety and Health Act of 1970, Civil Rights Programs of Equal Employment Opportunity, and added accounting controls and procedures. The issue of limitation on overhead rate also comes at a particularly trying time for many institutions suffering from severe income-cost squeezes.

HEW representatives report that the capability of the Department to negotiate fair overhead rates has been considerably eroded since the decentralization to the regional offices. Prior to decentralization, the Secretary's office included a group of fifteen to twenty fiscal experts, whose primary role was to negotiate with the more than 2,000 institutions doing business with the Department. This group was characterized as "tough, but fair." With the decentralization, they were assigned to regional offices, but most chose to retire or to take other jobs, leaving most regional offices without adequate capability. One NIH official associated with indirect costs who recently visited two regional offices reported that one was quite adequately staffed in this area, while the other was understaffed.

One problem in defining overhead rates is that the Department of HEW uses more than 100 ways of allocating it. For example, certain types of fringe benefits may be included in direct costs or indirect costs. The complexities make it very difficult to assess the fairness of the indirect costs. The Department may not do an adequate volume of business with most of its more than two thousand institutions to require one common definition of indirect costs, but if this could be achieved, it would indeed be a positive step forward.

Another complaint from some of the extramural staff is that sometimes the Indirect Cost Management System will change—generally increase—the overhead rates in the middle or end of the year. When this happens to a large grant, and it is retroactive, this could be the cause for an overobligation of funds. Some of the staff is still skeptical about the information generated by this system, and often spend time themselves checking to see if the rates are correct.

The issue of indirect costs and their financial accountability seems worthy of an indepth policy analysis.

Program Project and Center Grants

As can be seen in Table 11, centers, resources and other grants totalled more than $246 million in Fiscal Year 1974. This has grown from approximately $100 million in 1968. In Report No. 93–1146,

[49] Seggel, R.L., "Overhead: Rationale and Reality 1975," Presentation to the President's Biomedical Research Panel, April 29, 1975.

issued September 11, 1974, the Senate Committee on Appropriations expressed concern with quality assessment through the peer review evaluation of NIH program projects and center grant proposals, and questioned whether individual projects on such grants receive in-depth review. The NIH responded to this concern on February 27, 1975.[50]

The report points out that in Fiscal Year 1974, including contract monies, NIH allocated $371 million, or 26% of the extramural research budget to program projects and center grants. In Fiscal Year 1974, the average size of a program project or center grant was $221,000 (direct cost), compared to the average size of a regular research grant of $38,000 (direct cost). Regular research project grants average just over three years in duration, whereas program project grants and center grants are usually awarded with an intent to support the project for four to five years.

These data support the value placed upon this mechanism by NIH program administrators and by the Congress, which has frequently directed that NIH program expansion for a specific disease or health problem include the establishment of centers. The NIH study and a Rand Corporation study [51] indicate that peer review for program projects and center grants is adequate to assure scientific merit of the component projects and activities. This review generally involves a site visit. However, this is a very complicated activity, and NIH has decided to hold workshops every year for NIH staff members directly responsible for large grant peer review to exchange information and ideas related to such activities. One such workshop was scheduled for 1975.

Research Contracts at NIH

In addition to supporting research via the grants mechanism, NIH accomplishes part of its task by supporting mission-related activities in other institutions.[52] The major part of such contractual activities is conducted in universities, research foundations, and commercial and industrial organizations. This is called "collaborative research and development" because NIH is seeking collaboration with other organizations and institutions to accomplish certain goals. Several examples of this have been given previously in this report.

Contracts, rather than grants, are usually used for support of research and development when one or more of the following considerations exist:

> The awarding institute or division has identified a need for certain research work to accomplish its mission and has determined that the work must be done outside its own facilities. This is sometimes referred to as targeted research and the philosophy is that the NIH staff should look at the field of biomedical science and target funds to those areas which need further development or are ready for development. The objective is the acquisition of a specified service or end-product.

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[50] National Institutes of Health, "Program Project and Center Grants," Report to Senate Committee on Appropriations, February 27, 1975.

[51] Carter, G. M., *et al.*, "Peer Review Citations and Biomedical Research, Policy—NIH Grants to Medical School Faculty," Rand Corporation, December, 1974, p. 81.

[52] Much of the data in this section came from the "NIH Guide for Grants and Contracts," Vol. 3, No. 21 and "A Guide to the NIH Research Contracting Process."

The collaboration of a number of institutions must be obtained and the work must be carried out in a comparable manner so that the data collected can be combined for statistical analysis, such as in clinical trials.

The awarding unit participates in the direction and control of the work to the degree necessary to assure accomplishment of its objective.

Examples of these activities, separated by institute, are enumerated below:

National Cancer Institute—Clinical trials of drug combinations, and combinations of drugs with other modalities including surgery, radiotherapy, and immunotherapy have been sponsored. Screening of components for carcinogenesis has been carried out and field studies in population groups have been done under contract.

National Heart, Lung, and Blood Institute—Contracts have supported resource centers in which models of chronic atherosclerosis and hypertension can be developed. Solicited research has been done on such areas as sudden cardiac death and quantifying the size of myocardial infarction, and a national collaborative trial on coronary artery surgery was done. A large hypertension detection and followup program was carried out in fourteen communities. In the Division of Blood Diseases and Resources, trials have been initiated to test the usefulness of heparin and platelet inhibiting agents for the prevention of venous thrombosis in high rish groups. In the Division of Lung Diseases, contracts support studies in the pathophysiology of respiratory disorders.

National Institute of Allergy and Infectious Diseases—The Institute's Infectious Diseases branch promotes targeted research leading to the development and evaluation of promising prophylactic and therapeutic agents, in particular, vaccines. Current interests include development and evaluation of vaccines against pneumococcal pneumonia, meningococcal and hemophilus influenzae, meningitis, influenza, and other upper respiratory diseases.

National Institute of Arthritis, Metabolism, and Digestive Diseases—The artificial kidney chronic uremia program was established by the Institute in the fall of 1965 with funds earmarked by the Congress for a target oriented planned program of research and development in chronic uremia, dialysis, and the artificial kidney. Currently, about 70 contracts support carefully selected research development program elements.

National Institute of Child Health and Human Development—The Institute has various contracts in the area of contraceptive development and in the evaluation of existing contraceptive methods. In addition, contracts are give for social science research related to population.

National Institute of Dental Research—Much of the contract activity relates to the National Caries Program. Much of this research is targeted to the acceleration of the development of preventive methods for decreasing the incidence of dental cavities and making this disease almost completely preventable.

National Eye Institute—The National Eye Institute has supported considerable research and development in the area of

glaucoma since 1971, and in 1973 initiated a similar effort in the area of retinal disease.

National Institute of Environmental Health Sciences—Areas being studied include heavy metals toxicity, chemical mutagenesis, biological effects of microwaves and noise, and environmental factors associated with defects of reproduction and development.

National Institute of General Medical Sciences—Automation of the clinical laboratory has been a major area of interest. Subject areas include sample collection and labeling techniques, new and improved analytical methods and portable test systems for emergency use, all intended to increase reliability and clinical significance. In addition, research, development and evaluation is being carried out in all aspects of therapeutic drug use.

National Institute of Neurological and Communicative Disorders and Stroke—the collaborative perinatal project is presently carrying out an analysis of data collected on 50,000 pregnancies and the resultant neurological and mental development of the offspring. The Institute has also initiated programs of applied research on improved methods of detecting and diagnosing hearing loss in infants and children.

There are also times when the use of contracts becomes mandatory, such as when awards are made to commercial or industrial profit-making corporations (in which case grants are normally precluded).

Contracts offer more universal competitive opportunities to all types of scientific sources, and are used by the awarding agency as a means of fulfilling its program objectives. Because the government defines the areas of work to be undertaken by contract, offerors can compete for a commonly understood objective and contract proposals received are evaluated within the framework of technical evaluation criteria announced to all competing sources.

Contracts are awarded at the initiative of the bureaus, institutes, divisions, the Clinical Center, and the Office of the Director of NIH. Each must develop, review, and approve its own functional program requirements. Once a sponsoring organization devises a contract project for the implementation of an approved program, its staff develops the technical objectives, participates in the drafting of the Request for Proposal (RFP), evaluates the proposals, and makes recommendations regarding the acceptability of the proposals for negotiation and award.

A project officer from the sponsoring component is usually appointed with each contract award. He must be experienced in the contract project area, monitor the technical aspects of the project, and assist the contracting officer in the administration of the contract. The project officer has primary association with the contractor's principal investigator and aids him in the resolution of technical problems encountered during performance, if so requested.

The contracting officer is an officially appointed agent of the government who has the power to execute and/or amend the contract as a representative of NIH or any of its components. Each contract is negotiated and administered by an authorized NIH contracting officer or his designee.

The terms and conditions of NIH contracts are flexible enough to meet new or changed requirements as work progresses. The contract instrument itself provides the mechanism for the contracting officer and the contractor to agree on the changes in the work statement, expansion or reduction in the basic work requirements, and adjustment of funding levels.

Endeavoring to acquire the most advanced scientific knowledge available, NIH policy is to solicit contracts on a competitive basis to the maximum extent practicable. Depending upon the nature of the requirement, competition among qualified educational institutions and private organizations including small business firms is encouraged. Prospective sources may learn of planned NIH contract projects in the *Commerce Business Daily*. Notices placed in this publication inform the prospective sources whether they should request to be included in the list of sources to be mailed a formal RFP or whether they should respond with a resume of their qualifications and capabilities to perform the particular contract requirements. Planned NIH contract projects are also included in supplements to the "NIH Guide for Grants and Contracts," which is primarily distributed to educational and nonprofit institutions throughout the United States. Policy guidance as well as information concerning NIH programs is included.

Requests for Proposals (RFP) are issued by NIH contracting organizations and contain all of the information necessary to enable prospective contractors to prepare contract offers. It includes: the statement of required work, the desired performance schedule, the available government furnished property if any, the applicable contract provisions to be included in the contract as awarded, and the criteria which will be used by the government to evaluate the proposals received.

Also provided in the RFP is useful guidance to prospective offerors on how to present the technical portion of their proposals and how to prepare pricing data. A required date of submission which allows sufficient time to prepare and submit proposals is given. The RFP statements of work are specific enough to assure offerors that they are competing on some common basis, but are flexible enough so that the offerors are given reasonable discretion to present their own approaches to the contract objectives. The evaluation criteria mentioned in the RFP are used to bridge the gap between the RFP work statement and the anticipated diversified approaches to the problem.

Solicitations received in response to an RFP are evaluated by one or more panels of persons competent in the scientific disciplines associated with the contract requirements. The panels are normally comprised of *both* government and nongovernment reviewers who evaluate the proposals on the basis of evaluation factors announced in the RFP. Once the proposals are deemed acceptable, they are then reviewed from a business point of view. The various elements of the proposals involving costs are examined by government cost analysts in conjunction with technical personnel. In addition to determining overall cost reasonableness of the proposal, such analysis will disclose desirable shifts in emphasis by the offerors.

As a result of these two reviews, a competitive range is established which includes those proposals which have a reasonable chance of being selected for award. The contracting officer negotiates with these offerors providing them an opportunity to present for consideration

their positions with respect to any aspects of the requirement, schedule, and price to be paid. The ultimate objective of such negotiations is to reach a balanced equitable agreement. After negotiations, a proposal is selected for award which offers the greatest technical advantage to the government, price and other factors considered. In some instances, more than one award may be made under the same RFP.

After making the award to the successful offeror, the contracting officer will give written notice to the unsuccessful offerors that their proposals were not accepted. A notice of the award is also published in the *Commerce Business Daily*. Upon request, an unsuccessful offeror may receive a debriefing or explanation of the evaluation considerations that resulted in nonacceptance of his proposal.

In addition to contract projects which are planned and developed by the NIH program activity, unsolicited proposals can also be the basis for establishment of requirements to be obtained by contract. An unsolicited proposal is a voluntary offer by sources outside of the government of new ideas and concepts that the government may find meritorious and useful in furtherance of NIH programs. The unsolicited proposals may be the basis for a sole source contract when the content of the proposal represents the product of unique and original thinking by the originator and is relevant to program objectives. Or it may serve as the basis for the government's competitive solicitation of the subject matter contained in the unsolicited proposal, if the RFP in no way reveals truly original ideas or approaches of the originator.

Criticism of the contract mechanism focuses very much on the National Cancer Institute, which obligated more than $220 million in fiscal year 1974 in contract awards (see Table 11—sum of "Research and Development Contracts" and "Collaborative Research and Support"). This is more than half the contract money at NIH. It is alleged that contracts are not of the same scientific quality as grants, and that their award and monitoring is highly affected by favoritism between staff of the National Cancer Institute and specific investigators. This type of criticism has been directed against the National Cancer Institute since it first began to use the contract mechanism to support research. The issue has been publicly aired frequently and the National Cancer Institute and NIH have taken steps to try to assure the quality of contracts and objectivity in the awarding process.

While the philosophical debate regarding the justifications for contracts versus grants is a hard one on which to gain agreement, there *is* agreement on the need for adequate monitoring by NIH staff to assure successful contract performance. The stringent restriction on staffing increases at NIH has made it difficult to adequately provide for contract management. The Director of the National Cancer Institute (NCI) recently remarked that he would not be able to accept additional funding unless it was accompanied by additional positions to administer the programs.

The whole issue of the staffing needs for adequate contract monitoring could not be analyzed in this study, and therefore must be left as an unfinished matter in need of further study.

As noted earlier, another problem with contracts that has been repeatedly alleged is weaknesses in the review process. The NIH has been criticized for not having peer review of contracts, and presently

all contracts are said to be under peer review. On August 26, 1975, NIH had 32 committees authorized by their charters to review only contract proposals and 13 authorized to review both contract proposals and grant applications (initial review groups). The present peer review, however, is involved at the level of assessing proposals which come in response to an RFP, and generally not in the development of the RFP itself. Some feel that review of the RFP or involvement of a peer review group in the development of the RFP is actually more important than the review of the proposals themselves.

In addition, the national advisory councils to not review contracts. As previously stated, these councils need strengthening as a basic connection to the broader society, and should be more involved in developing priorities and programs for the institutes. Noting that the Ruina Committee recommended that the national advisory councils not review contracts, and that the contract mechanism in the National Cancer Institute was intended to shortcut time delays in getting projects underway, with the involvement of the Assistant Secretary for Health and the Secretary of HEW in the contract process, it takes from nine months to a year to let a contract—approximately as long as to arrange a grant. Therefore, the rationale for not having national advisory councils review contracts seems to have disappeared. If the councils are to be deeply involved in the programs of the institutes, it seems essential that they be aware of contract activity.

A problem area has surfaced with the Federal Advisory Committee Act and the contract review process, especially in the review of smaller contracts. The Act requires that each advisory committee be chartered before it can meet or take any action. Unlike the grant review mechanism, the contract mechanism calls for establishment of numerous *ad hoc* committees in addition to standing committees, to review specific contracts. Often, however, committees cannot be chartered in time to review the proposals in hand. Presently, in order to circumvent this regulation, NIH is using a very fine definition of the word "committee" and is seeking advice from individual reviewers instead of asking for a consensus of a review group—the group would have to be chartered as a committee under the Act, the individuals do not. This is the same procedure followed by the Food and Drug Administration and has been published by FDA in the Federal Register. Some NIH officials feel that NIH should have the authority to set up these *ad hoc* committees for contract review, and this appears to have some merit.

Another problem area brought forth by Cancer Institute personnel was that of one year funding and the contracting process. It is not uncommon for the staff to find that it has more money at the end of the year than it had planned on. Last minute spending in order not to lose the funds offers hazards to the prudent expenditure of public monies. The contractors know that NIH must obligate money before the end of the fiscal year, and this gives contractors, especially those bidding for construction contracts, an advantage in the negotiations. Some institute officials would like to see some amount of "carryover money," believing that this would make for better management, emphasizing that the contract review process is extensive and time-consuming.

CHAPTER 7

Research Training at the National Institutes of Health

Research training was not examined in great detail because of the unstable and changing nature of this activity. Nonetheless, a few observations can be made.

One of the traditional missions of NIH has been the training of biomedical research personnel, both in the NIH itself, and through grants to institutions and individuals. Authority for the training of biomedical researchers was first provided to the National Institute of Health in 1930. The original research training authority has been reaffirmed and expanded by legislation repeatedly since then. By 1971, NIH training grants and fellowships supported or assisted 37.5% of the Nation's full-time graduate students in the medical sciences and 21% in the life sciences.

The President's Fiscal Year 1974 budget initially proposed the phase-out of all biomedical research training grants and fellowships, which at that time were being funded at approximately $185 million a year. This decision was made at the Office of Management and Budget (OMB) which pointed to an excess number of qualified trained researchers as indicated by the number of approved but unfunded research grant proposals, and argued that no other group in the society has its training subsidized to the same extent. The old fellowship and training programs began a phase-out in January, 1973, but because of outside pressures the Administration modified its position and developed a limited post-doctoral fellowship program, the so-called Weinberger Fellowship Program, which was initiated in July, 1973.

The Congress supported a more expensive and inclusive program by the passage of the National Research Service Award Act (PL 93–348) of July, 1974. That law repealed all of the previous NIH research training authorities with the exception of existing commitments and consolidated them in a new mechanism called the National Research Service Award. Under this Act, the Secretary of HEW was directed to provide pre- and post-doctoral support to individuals, and additional support to institutions training such individuals. In addition, the National Research Service Award authority provided that recipients of support should be required to fulfill a service obligation as a condition of receiving support, and that research training support be directed to and made available to persons in specific areas in which a need for additional researchers had been determined. The Act provided a one-year appropriation authorization. Because of this new Act, NIH was unable to make any new fellowship or training awards after July 12, 1974, until the regulations governing the new program were finally published May 2, 1975, and with an appropriation, awards were subsequently granted.

The expenditure for training for Fiscal Year 1975 was approximately $115.1 million under the old training programs and $41.2 million under the National Research Service Award Act, for a total of $156.3 million.

Beginning July 1, 1975, institutes are only making awards to train investigators in fields determined to be in need of research personnel. The National Academy of Sciences is carrying out a study to determine such shortage areas but in its 1976 Report, the Study Committee did not make specific recommendations.[53] In the meantime, the National Institute of General Medical Sciences identified shortage areas using expert committees. The following areas were found to be in chronically short supply: (1) anesthesiology,. (2) biometry, (3) epidemiology, (4) genetics, (5) nutrition science, (6) pharmacology (chemical), and (7) radiology (diagnostic). NIH has been awarding fellowships to postdoctoral students in shortage areas and these have gone well beyond the seven shortage areas listed, as each institute is making its own list of shortage areas. Eventually, research awards will be made only to trainees in areas found by the National Academy of Sciences to be in short supply. There seems to be wide-spread consensus in the Congress, at NIH, in the research community, and in the Administration that some scientific areas are over-supplied with trained personnel.[54] There is also a clear need to achieve some sort of a steady state in most of biomedical research activities, since competing priorities make it unlikely that research monies will continue to expand as they have in the past. The obvious problem is whether the training system can be "fine-tuned" to that extent.

Table 14 illustrates the problem. In Fiscal Year 1974 there were 100 trainees in biochemistry, 180 in microbiology, 279 in pathology and so on. In contrast such shortage areas as epidemiology and environmental health had only 19 and 26 trainees respectively, and social science trainees were almost entirely lacking. These figures seem to point out the need for vigorous action in fostering the training of non-medical disciplines in biomedical research.

Despite the passage of the National Research Service Award Act of 1974, the Administration proposed, in its budget request for 1975 to eliminate predoctoral and institutional support and to severely limit the number of new postdoctoral individual awards. The Fiscal Year 1976 budget request was based on a Fiscal Year 1975 rescission proposal and would have allocated only $136 million for the funding of all research training for both NIH and the Alcohol, Drug Abuse, and Mental Health Administration. It was estimated that this would allowed only 1,000 new postdoctoral individual awards by NIH, compared with the 4,431 total postdoctoral traineeships and 7,076 predoctoral traineeships awarded in Fiscal Year 1974. The Congress rejected the 1975 rescission proposal, including the proposed cutback of research training activities.

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[53] National Research Council, "Personnel Needs and Training for Biomedical and Behavioral Research," The 1976 Report of the Committee on a Study of National Needs for Biomedical and Behaviorial Research Personnel, National Academy of Sciences, May 7, 1976.

[54] Braunwald, E., "The Training of Manpower Needed for Biomedical Research, *N.E.J.M.* 292: 290–293 1975.

TABLE 14.—NIH RESEARCH FELLOWSHIPS, AND TRAINEES UNDER RESEARCH TRAINING GRANTS, BY FIELD OF INTEREST AND ACADEMIC LEVEL, FISCAL YEAR 1974

[Dollar amounts in thousands]

Field of interest	Research fellowships [1]				Number of trainees (full and part time) under research training grants [5]		
	Number [2]						
		Postdoctoral				Postdoctoral	
	Predoctoral	Professional [3]	Academic [4]	Amount	Predoctoral	Professional [3]	Academic [4]
Total I/RD	114	616	1,538	$30,644	7,076	3,282	1,149
Health-related professions and activities	93	596	1,356	27,631	6,220	3,259	1,060
General medical and biological sciences	74	256	1,274	20,963	5,358	432	864
Anatomy	3	9	47	877	232	14	26
Biochemistry	12	31	375	5,147	1,138	16	84
Biophysics	3	6	71	960	421	2	51
Microbiology	22	56	227	4,044	905	29	151
Pathology	2	24	28	745	140	206	73
Pharmacology	4	29	87	1,758	490	34	98
Physiology	13	55	188	3,585	525	53	131
Genetics	5	19	66	1,069	378	19	76
Nutrition		3	14	195	87	1	3
Cell biology	2	13	71	1,031	129	2	24
Biology	7	7	54	902	264	20	56
Other	1	4	46	649	649	36	91
Clinical medicine	3	306	46	5,352	338	2,732	162
Internal medicine	2	173	14	2,808	149	1,234	120
Pediatrics		59	3	861	7	182	1
Obstetrics-gynecology		7		101		13	
Radiology	1	10	5	223	38	289	12
Surgery		21	1	289	6	256	7
Otorhinolaryngology		1	4	75	35	197	8
Ophthalmology		13	1	246	9	135	7
Anesthesiology		3		41		68	2
Neurology		9	14	413	11	342	4
Other		10	4	268	83	16	1
Clinical dentistry		8	3	$201	42	49	2
Other health-related fields	16	26	33	1,142	482	46	32
Engineering, health-related	15	5	14	467	254	12	8
Veterinary medicine		15	2	295	2	19	
Biostatistics	1		9	163	151		15
Epidemiology		5	6	163	62	15	4
Other		1	2	54	13		5
Community health fields					2		
Environmental health fields	2		5	136	90	6	20
Psychology	1	4	65	987	343	5	45
Social sciences		1	9	108	269	3	7
Sociology		1	4	55	128	3	5
Anthropology			4	44	123		2
Other			1	9	18		
Math, physical sciences, engineering, other	17	15	103	1,768	111	2	17
Chemistry	14		78	1,033	104	2	17
Other fields	3	15	25	735	7		
NLM	1			14	41	7	

[1] Includes fiscal year 1973/74 released funds.
[2] Represents number of awards, not number of persons.
[3] Holders of the M.D. or equivalent professional doctorate (D.D.S., D.V.M., D.M.D., etc.), including those holding both professional and academic degrees.
[4] Holders of the Ph.D. or equivalent academic doctorate (D.Sc., D.P.H., D.Eng., etc.).
[5] National Institutes of Health, Basic Data Relating to the National Institutes of Health, 1975. Training in fiscal year 1974 but paid from fiscal year 1973 funds.

The Administration's reluctance to support predoctoral-level research training has caused some concern in the Congress. It is from the predoctoral ranks that postdoctoral-level research scientists emerge. The Committee on Interstate and Foreign Commerce commented as follows: [55]

[55] Report by the Committee on Interstate and Foreign Commerce House of Representatives, "Heart, Lung and Blood Research, Research Training, and Genetic Diseases Amendments of 1975," Sept. 22, 1975

The Committee believes it is vitally important to support graduate students seeking the Ph. D. or a combined degree with a view to engaging in careers in biomedical or behavioral research. Not only should the supply of highly qualified Ph. D. candidates be maintained, but vigorous steps should be taken to attract bright young persons to careers as research scientists through programs of support for predoctoral training.

Furthermore, phasing out of predoctoral training as recommended by the Administration would remove research training support from such non-medical disciplines as social work, whose terminal degree is not a doctorate.

Another issue regarding research training is that of recruitment of minorities into biomedical research careers. Several informants at NIH, including one institute director, felt that such recruitment could be done more effectively if NIH were given the authority to support a limited amount of pre-Baccalaureate training for minority students. This would require a change in the statute. In addition, predoctoral support for minority students is important. It seems clear that minority recruitment into biomedical research careers should be a high priority and that action to permit this is needed.

The Administration position on institutional awards can also be questioned. Institutional awards are a vital mechanism in the overall research training effort. It is through such awards that institutions are able to build up and maintain excellent environments in which to train future scientists. In addition, the institutional award is made to the training institution which selects those to be trained and which is in the best position to weigh an applicant's merits and potential for a productive research career within the environment of that particular institution.

Perhaps the greatest overall problem facing the training area in the last several years has been that of instability. With the NIH not funding any programs for almost a year, some programs have essentially ceased operating. This has hit particularly hard at shortage areas. It is certainly to be hoped that with new statutory authority it will be possible to again develop a stable situation in which the research community and potential trainees may have confidence.

CHAPTER 8

Organization of the National Institutes of Health

Most observers of the NIH feel that the "categorical" structure of the institutes has been a key to the success of NIH. Though not totally logical or categorical, it has given the public, the Congress and the Administration a reasonably good way of understanding and identifying with the missions of each institute. In addition, the focus by institutes has made the relationship to practical disease problems easier and more salient for the basic biomedical researcher. The administrators of the scientific enterprise interviewed generally felt that although basic science cannot be specifically targeted, the researcher himself or herself needs continual contact with the real world of disease problems and continual reminders that the work must in some way have applicability to existing medical conditions. Indeed, it was impressive in talking to basic biomedical researchers at NIH to find an orientation toward eventual usefulness of their findings in preventing or ameliorating disease problems. Thus, categorical identification has definite merit. A problem, however, that NIH is facing is pressure for too much categorization. Specifically, categorical disease interests not represented by name in the institute structure are seeking new institutes to represent these problems, age groups, or fields. Recent examples are the National Eye Institute and the National Institute on Aging. With eleven institutes the problem of fragmentation becomes very real, particularly with two of those institutes, the National Environmental Health Sciences Institutes and the National Institute on Aging being located off the Bethesda campus.

This fragmentation is very much related to the NIH managerial function, and is fostered by the individual appropriations to each institute. Furthermore, two of the institutes, the National Cancer Institute and the National Heart, Lung, and Blood Institute, are bureaus in the Public Health Service, as is the National Library of Medicine, and this causes resentment in the other institutes.

The differences in the institutes in the way that they carry out their business, in the philosophy of the staff in different institutes, and in the mechanisms used are striking. Part of this is defined in statutes, as in requirements for specialized centers and in the statutory authority of the National Institute of Dental Research to work directly with States. In other instances, the institute has made the determination. For example, as will be described later in this Chapter, the National Institute of Allergy and Infectious Diseases has a special mechanism for setting research priorities. The internal organization of the different institutes is sometimes by funding mechanism (intramural, extramural grants, and extramural contracts) and sometimes by program. (See Appendix 2) The NIH, with its eleven institutes, represents a natural experiment in the administration of science which deserves evaluation. Ineffective mechanisms should be dropped and successful innovations fostered.

LEADERSHIP

The leadership of NIH has been a problem, as mentioned previously, since 1968, when Dr. Shannon left. Many observers see NIH as passively awaiting events, reacting to events imposed from the outside, and failing to develop active programs in areas of need.

The legal role of the Director of NIH is as the overall administrator of programs and activities and as the manager of the Bethesda campus. This in particular requires his ability to relate to the scientists in the intramural program. He must speak as a member of the health team of the Assistant Secretary of Health. Finally, and in some ways most important, he must lead in the development of health research policy, both within the Executive Branch and as a spokesman for the biomedical research community.

The Director has control over institute budget requests, except for that of the National Cancer Institute, legislation, hiring and firing of institute directors, top-level promotions, etc. However, his power often depends greatly on persuasion and moral leadership. As noted earlier, funds are appropriated not to NIH centrally, but to each institute as a separate appropriation. Some feel that the Director should be given greater powers by statute or regulation. Others feel that he has all the power he needs if allowed to exercise it by the Department of HEW and OMB.

The issue of the strength of the leadership of the Director of NIH is certainly an important one, and deserves further attention.

THE STATUTORY BASE FOR NIH

As previously noted, the different institutes have quite different statutory bases. Two institutes, the National Cancer Institute and the National Heart, Lung, and Blood Institute, have renewable authorizations with monetary ceilings. Other institutes have authorizing statutes with no time or money limitation. One institute, the National Institute of Environmental Health Sciences, has no specific authorizing statute, but depends on Section 301 of the Public Health Service Act.

One value of a time-limited authorization is that it allows the institute director an added opportunity to bring his problems and accomplishments before the Congress and the American people. Another general advantage would be to have all institutes on a common statutory base. Finally, the renewal process of authorizing legislation allows Congressional oversight and modification of programs and promotes accountability to the Federal taxpayer. Such a change is worth considering.

PRIORITIES

Although many in the scientific community would reject the idea of prioritizing science, there is in fact a very complex system of priority setting already in operation at NIH and in NIH's relation to the outside world. These priorities begin, of course, with the establishment of specific institutes by the Congress and by the authorization and appropriation levels for those institutes or programs. The question is often posed concerning the relation between those gross priorities and health problems in this country. Table 15

gives a calculation of total economic cost for different categories of disease. This indicates that neoplasms (cancer) cost considerably less than diseases of the circulatory system, which are mostly heart diseases. Measures of health such as days of hospitalization also indicate that heart disease is considerably more important than cancer in its impact on health. On the other hand, Cooper and Rice [56] point out that pain and suffering have not been quantified as a dimension of illness, and a Gallup poll conducted in 1972 indicated that 82% of the population identified cancer as the greatest health hazard. The scientific community tends to reject the idea of setting priorities on the basis of such information, feeling that the "state of the art" in science and having good people in the field are the critical variables in producing good research.

TABLE 15.—TOTAL ECONOMIC COST: ESTIMATED DIRECT EXPENDITURES, INDIRECT COSTS OF MORBIDITY AND PRESENT VALUE OF LIFETIME EARNINGS DISCOUNTED AT 6 PERCENT, BY DIAGNOSIS, 1972

Diagnosis	Amount (millions)				Percentage distribution			
			Indirect costs				Indirect costs	
	Total	Direct costs	Morbidity	Mortality	Total	Direct costs	Morbidity	Mortality
Total	$174,934	$75,231	$42,323	$57,380	100.0	100.0	100.0	100.0
Infective and parasitic diseases	3,234	1,412	1,200	622	1.8	1.9	2.8	1.1
Neoplasms	15,641	3,872	862	10,907	8.9	5.1	2.0	19.0
Endocrine, nutritional, and metabolic disease	5,717	3,436	1,137	1,144	3.3	4.6	2.7	2.0
Diseases of the blood and blood-forming organs	875	491	220	164	.5	.7	.5	.3
Mental disorders	13,782	6,985	6,179	618	7.9	9.3	14.6	1.1
Diseases of the nervous system and sense organs	10,703	5,947	3,944	812	6.1	7.9	9.3	1.4
Diseases of the circulatory system	37,430	10,919	6,417	20,094	21.4	14.5	15.2	35.0
Diseases of the respiratory system	15,764	5,931	7,089	2,744	9.0	7.9	16.7	4.8
Diseases of the digestive system	16,931	11,100	2,606	3,225	9.7	14.8	6.2	5.6
Diseases of the genitourinary system	6,344	4,471	1,249	624	3.6	5.9	3.0	1.1
Complications of pregnancy, childbirth, and the puerperium	2,914	2,607	245	62	1.7	3.5	.6	.1
Diseases of the skin and subcutaneous tissue	2,040	1,525	460	55	1.2	2.0	1.1	.1
Diseases of the musculoskeletal system and connective tissue	8,913	3,636	5,103	174	5.1	4.8	12.1	.3
Congenital anomalies	1,375	331	238	756	.8	.5	.6	1.3
Accidents, poisoning, and violence	21,649	5,121	3,883	12,645	12.4	6.8	9.2	22.0
Other	11,625	7,398	1,494	2,733	6.6	9.8	3.5	4.8

Source: Table 7 in Cooper, B.S. and Rice, D.P. "The Economic Cost of Illness Revisited," presented at the American Public Health Association Meetings, Chicago, Nov. 20, 1975.

TABLE 16.—ESTIMATES OF PEER GROUP PRIORITY CUTOFF SCORES FOR FUNDING NIH RESEARCH GRANTS

[The lower the numerical score, the higher the quality of grants funded]

Institute	1972	1973	Estimate, 1974	Present, 1975 (estimate)
Cancer	286	256	265	200
Heart/Lung	267	242	260	250
Dental	279	291	253	220
Neurology	225	225	250	215
Allergy	232	235	220	185
General Medical	235	208	205	185
Child Health	280	207	286	200
Eye	261	241	250	220
Environmental Hea th	243	220	210	190

Source: "Health Program Memorandum and Discussion of Budget/Legislative Issues, 1976–80, "Assistant Secretary for Planning and Evaluation, DHEW, July 1974.

[56] Cooper, B.S. and Rice, D.P., "The Economic Cost of Illness Revisited," Presented at the American Public Health Association Meetings, Chicago, November 20, 1975.

The National Cancer Institute is sometimes criticized for not supporting high quality research. In fact, however, Table 16, which shows priority cut off scores for funding of NIH research grants indicates that cancer is actually funding high priority research and falls somewhere in the middle range of the institutes in general. A study by the Rand Corporation [57] indicates that good scientists have switched into the field of cancer since 1971. Thus it seems reasonably clear that priorities can be set to some extent for research, and that since taxpayer monies fund the research, it is appropriate for Congress to be involved. The most important reason for this, perhaps, is that scientists seem to focus on rare diseases more than might be desirable.

Since resource allocation is at best a developed art, it seems clear that the optimal situation is a dynamic one, with NIH and the Administration interacting with the Congress, allowing specific disease interests and the public maximum input to the process. It should be stressed again that an active leadership for NIH, bringing the best scientific advice possible, is critical if the outcome is to be the best possible.

Within institutes, there are also potentials for setting priorities. As previously mentioned, this should be a function of the national advisory councils. However, it is not an easy function to operationalize. One institute director observed that one member of his advisory council tended to choose one proposal which would not have been otherwise funded, and because of the force of his personality, could convince the remaining members of the national advisory council to fund that proposal. An alternative has been developed in the National Institute of Allergy and Infectious Diseases.[58] The Institute has what it calls a "dollar allocation for program areas" (DAPA). Each year the staff of the Institute studies the field of science and the problems in the infectious disease area and develops a list of areas which could profitably be emphasized. These are then discussed with the National Advisory Council of the Institute and a final list of ten or eleven areas is prepared with specific dollar allocations for each area. The total allocation for these emphasis areas is approximately 10% of all the grant money for the Institute. The National Advisory Council then reviews grants in its usual way, and generally assigns the first 90% of the available monies strictly on the basis of scientific merit as determined by the study section. However, the remaining 10% is then used to fund proposals which by study section assessment would not otherwise have been funded, but which are approved and which fall into the priority areas. Recent priority areas include hospital-associated infections, venereal disease, and hepatitis. This mechanism should be evaluated for consideration of extension to other institutes.

COORDINATION AND COMMUNICATION

Questions are often raised about coordination of research work within the NIH and with other research and regulatory agencies and institutions. The question of communication is related. One type of

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[57] Carter, G.M., *op.cit.*, p. 59.

[58] Davis, D. J., "Are Research Priorities Desirable," Remarks Made by the Director of the National Institute of Allergy and Infectious Diseases to the American Society for Microbiology, October 27, 1970.

question relates specifically to the research effort itself, with the key question being, "Do scientists within NIH and within other government institutions share results and work together adequately?" The other type of question deals with the use of research results in funding, as with Medicare, in regulation, as with the Environmental Protection Agency, and in other government activities. There are also duplications and confusions of role.

On the question of the research itself, the degree of informal interaction among scientists at NIH is impressive. It is often commented upon that each intramural program has a biochemistry group. There apparently have been some attempts to centralize such basic laboratory research, but these have not worked very well, and it seems to work better to have each institute set up an operation and then encourage maximum communication between the scientists themselves. Four or five interactions between scientists were observed, as were extensive conferences, involvement of scientific directors, etc. This does not seem to be a problem. There is on occasion some degree of duplication and overlap and competition. For example, the National Institute of Dental Research was the first to have a genetics program, but eventually other institutes became involved in genetics and the program of that Institute was terminated. This type of competition is probably healthy, provided NIH and institute management observe it and demand that convergence occurs.

In terms of coordination and communication with scientists from other agencies, little seems to occur directly. Scientists rely very much on the scientific literature and upon scientific meetings to keep up with their fields. Perhaps there should be more communication between government scientists in different agencies, but it is difficult to see how this could be effectively dictated. A much more serious problem is that of use of research findings by other government agencies. The regulatory function in particular is a problem. For example, environmental carcinogens are regulated by four agencies: 1) Food and Drug Administration, 2) Environmental Protection Agency, 3) Occupational Safety and Health Administration, and 4) Consumer Product Safety Administration. The National Cancer Institute has the responsibility for determining carcinogenicity and then communicating this to the appropriate agency. However, there are presently about 35 chemicals and classes of chemicals known to be carcinogenic, and 21 are said to still have significant population exposure in this country. In short, they are not being effectively regulated.* In one ambitious attempt to achieve effective coordination, the National Cancer Institute Director chairs an HEW inter-agency coordinating committee on cancer and also a new coordinating committee of the 16 Federal agencies dealing with cancer which will meet for the first time in the Fall of 1975. These committees seem to have potential value as communication mechanisms, but are not necessarily guarantees that the task will be fully accomplished.

In funding programs, very little communication takes place. As mentioned earlier in this report, a procedure shown to be ineffective by a controlled clinical trial at NIH could still be paid for under Medicare and Medicaid.

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* This situation is described in a forthcoming report from the General Accounting Office, "Federal Efforts to Protect the Public From Cancer Causing Chemicals Are Not Very Effective."

There are confusions and duplications in the roles of different agencies. In particular, one can point to the programs of NIH and those of the National Center for Health Services Research. It seems inevitable that NIH will become more and more involved in health services research, although it is far from clear that NIH has the disciplines necessary to carry out such research. The definition of health services research seems logically to include many types of clinical trials. Assessment of technology such as coronary care units could be done logically by either agency.

Finally, the role of the National Center for Health Statistics is an important one. Large amounts of data are collected at NIH which are not well-coordinated with other data-collecting activities. On the other hand, evaluation of the fruits of research and epidemiological research itself which NIH might fund need considerably better data systems. The National Center has been responsive to these concerns, stating that the most significant challenge is the "development of data systems that are capable of satisfying the multiple needs for data at the State and sub-State levels, and that provide the types of data needed for evaluation of the impact of major Federal health programs." [59] The Center's proposal to increase the size of the National Health Survey's Household Interview Survey addresses itself to the need for better morbidity data.

The Center has also proposed that it establish a reimbursable work program for special studies, especially on request of other Federal agencies, and that it expand its research program to emphasize epidemiological research. These new activities will require expansion in the very modest budget of the National Center ($35 million).[60] One possibility would be for the Department of HEW to channel some of the mandated 1% evaluation funds to the Center. In any case, this program certainly should be expanded.

The mechanism for carrying out coordination and communication in such areas is far from clear. There are many inter-agency coordinating committees functioning. But their effectiveness seems to be limited.

This is a problem in general that NIH personnel tend to deny exists. But the investigation demonstrated that it is indeed a very serious problem in need of considerable attention.

RELATIONSHIP OF NIH TO THE DEPARTMENT OF HEW

During the early days of NIH, and even into the 1960's, NIH made up a very large proportion of the Federal health activity. That situation has changed. NIH is now only one of six agencies of the Public Health Service, and is far over-shadowed by the quick growth of health expenditures in such programs as Medicare and Medicaid. This has led to new problems to which longtime NIH staff have had difficulty accommodating. In previous years, NIH related directly to the Secretary of HEW and to his staff such as the Comptroller or the Assistant Secretary for Administration. Now, there are few people left in the upper levels with whom NIH staff directly interface.

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[59] Assistant Secretary of Health, DHEW, "Forward Plan for Health," June, 1975.
[60] Inglefinger, F.J., "National Center for Health Statistics," *N.E.J.M.* 298: 1142–1143, 1973.

With the HEW reorganization, all communications are expected to flow through the Assistant Secretary's office. There is a widespread feeling among administrative staff at NIH that the Assistant Secretary's office has become involved in administrative tasks which fall more appropriately within the purview of the NIH staff. Although this problem apparently needs attention, the issue of NIH access to HEW management must be viewed as an issue internal to HEW. As will be mentioned in Chapter 10, NIH staff perception of these problems has led some to support a separate Department of Health.

CHAPTER 9

Management and Administrative Problems at the National Institutes of Health

NIH is suffering from several acute management and administrative problems which are probably not the result of conscious policy. Therefore, it seemed appropriate to highlight these problems in a separate chapter.

PERSONNEL CEILING

Over the nine year period, 1968 to 1976, appropriations for NIH programs have increased by 768 million dollars while the number of NIH personnel has declined by 540 positions. Table 17 shows the numbers of permanent personnel at NIH by institute and program over time. Figure 2 shows graphically the budget of NIH and the number of personnel over time. In particular, it shows that the NIH budget has increased considerably since 1971 with an overall reduction in personnel. The fiscal year 1975 ceiling was 10,451, which was 165 below the previous ceiling.

The personnel ceiling is imposed by the Office of Management and Budget (OMB) at the level of the Department. The Department then allocates positions between its different component parts. Thus, although OMB's position that it does not determine the number of positions at NIH [61] is technically correct, the decline of personnel positions at NIH is directly attributable to OMB policy.

NIH PERSONNEL AND BUDGET OBLIGATIONS
(1961–1976)

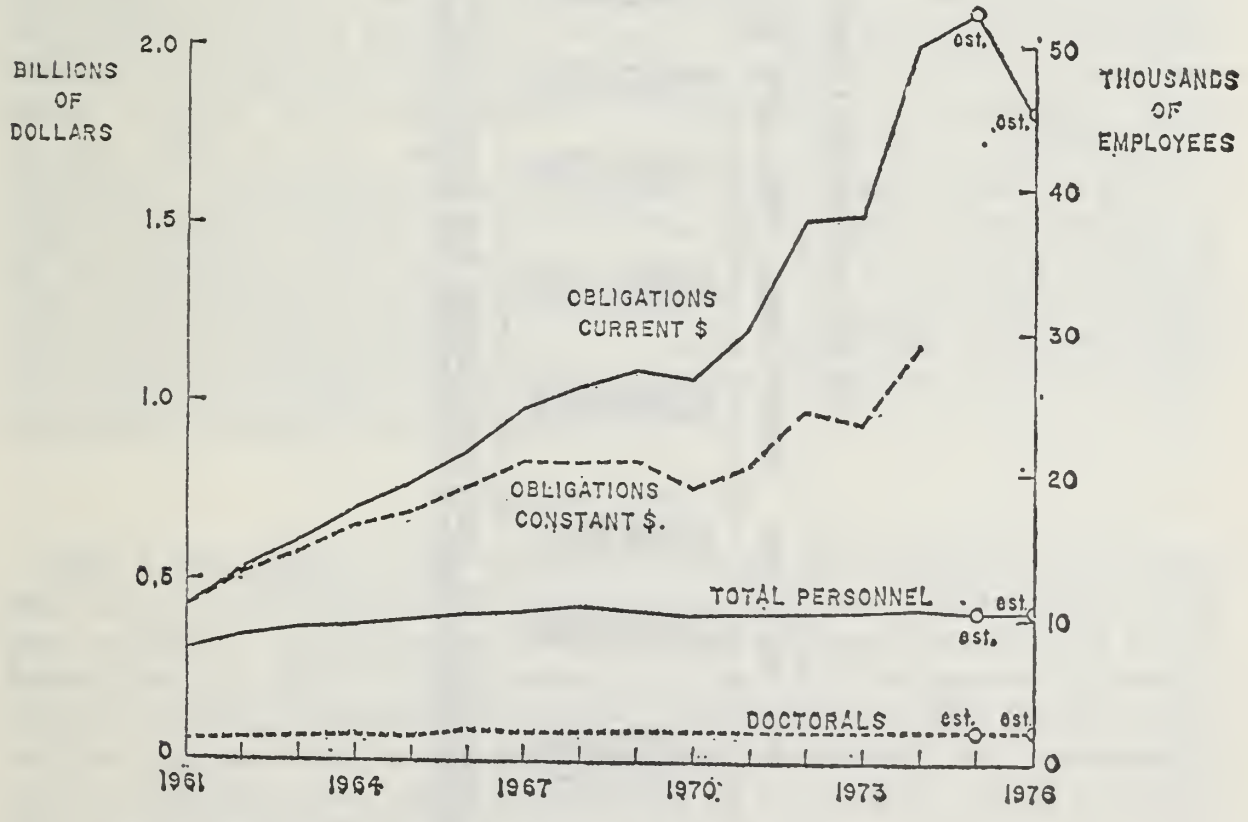

FIGURE 2

[61] O'Neill, P., Associate Director, OMB, Presentation to the President's Biomedical Research Panel, June 30, 1975.

NIH FULL TIME PERMANENT PERSONNEL 1968-75. BY INSTITUTE OR ORGANIZATION

Fiscal year	NCI	NHLI	NIDR	NIAMDD	NINDS	NIAID	NIGMS	NICHD	NEI	NIA	NIEHS	RR	FIC & NLM	DCRT	DRS	OA/PD	CC	DRG	Total
1968	1,453	619	301	633	732	706	207	405			169	148	553	314	624	2,010	1,580	537	10,991
1969	1,411	564	291	615	711	695	191	400			176	135	535	302	592	1,949	1,476	459	10,502
1970	1,355	558	283	588	588	676	180	415	85		202	82	509	284	572	1,888	1,443	425	10,133
1971	1,426	584	289	597	583	665	164	435	92		220	83	509	281	552	1,893	1,461	417	10,251
1972	1,665	618	288	585	557	623	167	482	117		235	78	524	270	529	1,843	1,395	407	10,383
1973	1,736	647	290	584	534	610	150	516	122		230	75	513	266	529	1,874	1,434	398	10,508
1974	1,805	689	269	560	530	595	135	519	128		237	71	517	251	530	1,869	1,518	393	10,616
1975	1,818	683	262	556	515	585	148	512	131		240	69	506	261	531	1,790	1,467	377	10,451

Note: RR—research resources; FIC—Fogarty International Center; NLM—National Library of Medicine; DCRT—Division of Computer Research and Technology; DRS—Division of Research Services; OA/PD—Office of Administration/Program Development; CC—Clinical Center; DRG—Division of Research Grants.

The fact that limitations on personnel have resulted in the inability to carry out programs established by law is amply demonstrated by the following excerpts from the NIH Forward Plan: [62]

1. The new NICHD Perinatal Wing in the Clinical Center will not be opened.
2. The National Arthritis Act of 1974 cannot be effectively implemented. In fact, it is impossible to initiate an intramural orthopedic research activity as mandated by the Act. Furthermore, the increased arthritis research under the Act cannot be effectively mounted since only a skeleton staff can be provided.
3. The National Diabetes Mellitus Research and Education Act, provided with a very minimal and inadequate implementation staff in 1974 will not receive any new positions in 1975.
4. To carry out improved research on kidney diseases and for basic clinical support, a medical nephrology service in the Clinical Center should be established. Under current employment restrictions, no positions are available to provide this service.
5. The National Institute on Aging can be provided only five new positions to start off the new Institute. This may be responsive to the basic need to start the Institute, but indefensible in terms of the core personnel required to meet the Congressional mandate.
6. General management and research support levels encompassing, in part, Clinical Center patient care, research services, facilities maintenance and contract and grant processing are at an abnormally low level in relation to the program need for such support. The NIH cannot pay its bills on time, has recurring and critical problems of inadequate patient care, cannot keep the buildings cleaned and maintained at an acceptable level, and cannot provide fully responsive support services to the scientific staff.

Thus, OMB, HEW, and NIH decisions and commitments related to the use of existing positions are obviously hampering the initiation of new efforts authorized by the Congress and have the same effect as the clearly illegal practice of impounding funds appropriated by the Congress. The easiest and most common response of agencies such as NIH to such criticism is that implementation of new programs is impossible without position increases. The time available for this study did not allow adequate assessment of this response. The biggest issue for revising the utilization of existing personnel, such as cancelling lower priority intramural efforts. In particular, as previously mentioned, NIH has not used opportunities to terminate unproductive programs involving tenured scientists. The same could be said of other personnel. In addition, the NIH campus contains many examples of tasks which could be contracted out instead of being maintained with career service personnel incumbency. It is a policy issue whether this should be done in preference to furnishing NIH with additional positions. An in-depth study of the personnel situation seems essential, and should be initiated in the near future.

SALARY ISSUES

The top salary for GS schedule civil service positions is $37,800 per year. For Public Health Service Commissioned Officers the scale goes as high as approximately $44,000, plus fringe benefits and allowances. Because the GS level ceiling has been held constant for several years, with only one recent increase, lower and lower GS levels qualify for the top pay level each year. This has led to problems in retaining staff and even more serious problems in recruiting senior scientific and management staff.

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[62] National Institutes of Health Forward Plan, Fiscal Years 1977 to 1981, April 30, 1975, pp. 4-1-2, 4-1-3.

Many individuals were interviewed at NIH who were at that upper level. The dedication of these individuals was very impressive. Virtually everyone reported that he or she had been offered a job at considerably higher salary within the past year. Indeed, Dr. Thomas Chalmers, formerly Chief of the Clinical Center, reported to the Committee on Interstate and Foreign Commerce that if he had not left NIH about two years ago, income taxes plus the cost of educating his children would have left him about a dollar a year to live on.[63]

The crisis in attracting and retaining the staff necessary to the NIH mission exhibits itself most clearly and dramatically at the very top levels of the agency. NIH cannot compete successfully with other organizations within the biomedical community, principally the medical schools, because of the salary limitation. The irony is that stipends for clinical investigators in medical schools have been driven up by government programs, especially Medicare and Medicaid, and by the fact that these investigators can be funded by NIH grants up to the level allowed by their institutions.

The 1973–1974 medical school faculty salary study by the Association of American Medical Schools reveals that department chairmen in medicine are paid base salaries that average $49,700. Chairmen of anesthesiology, pathology and radiology departments receive $40,000 to $55,000. In addition, most of these physicians can gain supplemental incomes from outside medical practice and consultation. It is also worth noting that university systems generally provide superior fringe benefits such as free health insurance and in particular tuition support for college-age children.

Positions which were vacant in July, 1975 included the directorship of the National Heart, Lung, anf Blood Institute and the directorship of the National Aging Institute. With the departure of the directors of the National Institute of Dental Research and the National Institute of Allergy and Infectious Diseases in July, four directorships were vacant.

NIH has recently completed a study of this situation which confirms the seriousness of the problem, and the large number of administrative positions which cannot be filled. primarily because of the salary ceiling.[64] Different institutes have complied lists of individuals who have turned down offers, citing salary differential as the main problem. The National Institute of Child Health and Development has listed eighteen recent refusals. There are at present at least 12 physicians in the National Cancer Institute who are considering offers at considerably more than their 1975 salary of $37,800.

One peculiarity in this situation is that Commissioned Corps personnel can make considerably more than the $37,800 ceiling and in fact, can make considerably more than the Director of NIH. With benefits such as free medical care and a non-contributory retirement plan, an incentive pay of up to $350 a month for a physician or dentist, $250 quarters and subsistence fee which is tax free, plus three months base pay for a promise to stay another year, a commissioned officer

[63] Chalmers, T.C., Testimony Presented Before the House Subcommittee on Public Health and Environment, Interstate and Foreign Commerce Committee, April 21, 1975.

[64] Division of Personnel Management, "Difficulties in Recruitment and Retention of Senior Staff at the National Institutes of Health NIH, June, 1975.

can make approximately $44,000. This is probably not competitive, but is certainly helpful. The latter amount, the variable incentive pay or so-called "physicians' bonus," was only implemented beginning in September, 1974 so it is too early to make an assessment of the successes of the program. However, it is interesting that 22 civil service medical officers employed by NIH have recently converted to the commissioned corps status since that program began, and their pay generally exceeds the $37,800 limit.

It is recognized that this is an important problem affecting NIH and other health agencies as well in their attempts to recruit physician manpower.

OTHER STAFFING PROBLEMS

The NIH has traditionally been an effective training institution for young biomedical researchers through the "NIH Associate Training Programs." Under these programs, young medical school graduates have entered NIH for two years as either research associates or clinical associates, and this has been one of the major recruitment mechanisms for younger scientists into NIH. One of the major incentives for application to NIH was the doctors' military draft and with its end there has been a great falling off of applicants for the associates programs. Applicants for the 1974 associate's programs number 171 for approximately 94 openings, as compared to a ratio of approximately 4 to 1 in previous years, as shown in Table 18. This has been particular hard on the anesthesia program, rendering it necessary to contract for anesthesia services on a rather expensive basis. It appears that there may be difficulty filling clinical positions, which might require cutbacks in research programs and patient care activity. There is still a surplus of research-oriented physicians, fortunately, and apparently no difficulty in recruiting young Ph.D. scientists.

TABLE 18.—NIH ASSOCIATE PROGRAM APPOINTMENTS, CALENDAR YEAR 1968–74

Program year	Applications received	Number interviewed	Number appointed
1968	755	507	201
1969	728	544	204
1970	522	395	202
1971	705	502	204
1972	583	454	242
1973	287	206	144
1974	171	140	94

Source: Division of Program Management, NIH, July 25, 1975.

SPACE

Due to space limitations on the Bethesda reservation, NIH leases space off-campus for offices and laboratories. Presently NIH leases approximately 505,000 square feet of space at six major locations in the Washington Metropolitan Area. On-duty personnel at the locations total about 2,300. A listing is given in Table 19.

The question as to how efficiently programs can be operated when the scientists and the administrators are physically separated must be raised. Daily interaction is impeded and a great amount of time can be spent travelling from one location to another.

NIH's Space Management Branch recognizes this problem and notes that if NIH were to construct all of the buildings already

planned for the Bethesda Campus, almost all of the staff could move in from these off campus locations, including 1,180 people from the Westwood Buildings.

While no specific recommendation is being made with respect to the present policy of rental of buildings, the rental policy should be thoroughly reviewed in connection with the present freeze on construction funds imposed by the Department to assure that a penny-wise, pound-foolish situation does not exist.

TABLE 19

Organization	Net square feet	On duty personnel (May 1975)	Annual rental cost	Lease term
Auburn Bldg., 4915–21 Auburn Ave., Bethesda, Md. (lab space):				
NICHHD	11,498	40		
NIDR	2,890	10		
NINCDS	2,794	9		
Total	17,182	59	[1] $156,404	1979
Blair Bldg., 8300 Colesville Rd., Silver Spring, Md. (office space): NCI	44,473	201	173,944	1977
DANAC Warehouse, 12725 Twinbrook Pkwy., Rockville, Md.: DAS/MM	57,807	15	[1] 116,400	1978
Federal Bldg., 7550 Wisconsin Ave., Bethesda, Md. (office space):				
BHRD/HRA	49,275	182	538,128	([2])
NINCDS	31,483	145		
NLM	5,944	35		
Total	86,702	362		
Landow Bldg., 7910 Woodmont Ave., Bethesda, Md. (office space):				
NCI	38,815	235	[1] 695,204	1982
NICHHD	27,186	160		
NHLI	17,262	113		
DAS	2,673	2		
BCSE	1,478	4		
Total	87,413	514		
Westwood Bldg., Westwood Bldg. Annex, 5331 Westbard Ave., Bethesda, Md. (office space):				
NCI	25,865	145	[1] 1,256,388	1978
NHLI	17,805	112	[1] 352,044	1978
NIAID	8,780	52		
NIAMDD	11,257	82		
NIEHS	1,158	3		
NIDR	15,045	87		
NIGMS	22,998	106		
NINCDS	11,818	69		
DRG	74,298	421		
DFM	8,994	62		
CPHS	4,665	20		
OGC	1,886	8		
DAS	6,568	13		
Total	211,137	1,180		
Total	504,714	2,331		

[1] Standard level user charges which is in excess of the actual costs to the government under the terms of the lease.
[2] Government owned.

Source: NIH Office of Administration, Space Management Branch.

BUDGET ISSUES

The budget issues are an example of a problem promoting instability and uncertainty at NIH and in the biomedical research community. In December 1974, the President submitted to Congress a plan to defer certain obligations in order to restrain 1975 budget outlays. On December 7, 1974, the President signed a 1975 appropriations

bill which provided an increase over the President's 1975 budget request. In January 1975, the President submitted to the Congress a proposal to rescind the additional amounts appropriated by Congress plus a portion of the President's 1975 budget request. While the recission proposal was being developed, NIH was notified that since recissions do not become effective unless approved by Congress, it would be required to obligate the funds before the close of the fiscal year for those recissions which were not approved. NIH was advised to carry out the normal activities leading up to the point short of obligating the funds. Thus NIH was faced with the task of developing plans for the remainder of the fiscal year to accommodate either meeting the requirements of the deferrals and recissions or obligating the funds if Congress should not approve these actions. In March, 1975, the Congress rejected the recission proposal. The impact of this situation was that NIH was confronted with the problem of obligating an additional $351 million dollars in the fourth quarter of 1975. While such situations are products of the national political situation, for which no pat answers can be stated, this example is cited to demonstrate the disastrous effects which such machinations have on biomedical research administration. Hopefully, the new Congressional Budget Act may improve the situation.

THE NATIONAL CANCER INSTITUTE BUDGET

Under the National Cancer Act, the National Cancer Institute submits its budget justification directly to OMB. However, in the course of compiling this budget justification numerous changes are required based on directions from the Assistant Secretary of Health and from the Department. The National Cancer Institute's staff is reluctant to submit or justify data which is at variance with its own estimates. Staffing levels are a particular problem. The Cancer Institute has the authority to submit requests for a position directly to OMB but the general feeling at NIH is that the Congress still intended for the positions of the Cancer Institute to be dealt with as part of the departmental total.

This process is disruptive to NIH as an institution although the National Cancer Institute has been quite cautious about insisting on its prerogatives. The matter deserves further policy level consideration.

THE NATIONAL COMMISSION FOR PROTECTION OF HUMAN SUBJECTS

The protection of human subjects in biomedical experimentation has been an active concern of the Federal government at least since the passage of the Kefauver-Harris amendments to the Federal Food, Drug, and Cosmetic Act 1962, which required informed consent of human subjects prior to their participation in drug testing. Concern for such subjects grew steadily up to publication of regulations for the Protection of Human Subjects of Biochemical and Behavioral Research on May 30, 1974.

Congress continued to express concern over the years, and after several series of hearings, the National Research Act was enacted in

1974. Title II of the Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Among other topics, the Commission is to identify basic ethical issues associated with biomedical and behavioral research, develop guidelines for the conduct of research, and study the ethical, social and legal implications of advances in biomedical and behavioral science and technology.

CHAPTER 10

Possible Congressional Actions With Reactions of NIH Personnel

During interviews with NIH personnel, reactions were sought to a range of possible Congressional initiatives. The purpose of this Chapter is to summarize these possibilities and those reactions.

1. *Nature of the statutes.*—At this moment, two Institutes have time-limited and dollar-limited authorizations. At least one institute has no specific statute. Should all the institutes have a similar statutory base?

(*a*) Should there be one statute for all of NIH, with goals and mission elaborated? Most favored this, but felt it would not be feasible politically.

(*b*) Should each institute have its own statute, with time and dollar limits? Most were ambivalent about this possibility, seeing both advantages and disadvantages. On balance, the reaction was mildly positive.

2. *Relation of NIH to the Department of Health, Education, and Welfare.*—Would a separate Department of Health improve the situation? Most felt this would be little improvement, although a few were very enthusiastic. Most raised practical difficulties, such as the importance of the welfare activity for health programs.

3. *Leadership.*—The leadership function has been eroded during the last seven years, and most favored action to strengthen it.

(*a*) Should the Director have tenure? There was great enthusiasm for this idea, with a five year term seeming most desirable.

(*b*) Should the Director be appointed by a group of peers from the scientific community? Most felt that this was neither feasible nor desirable.

(*c*) Should the Director have legislatively-mandated powers? Most felt that the individual in the Director's position was more important, and that this would make little difference.

4. *Balance.*—Should the resources available to certain institutes or programs be increased? Most felt that the Cancer Program is relatively over-funded. The National Institute on Environmental Health Sciences was felt to be the most under-funded institute. Programs in epidemiology, nutrition and family planning were felt to be the most under-funded.

5. *Salary.*—Should NIH be granted an exemption from the salary ceiling, as appears to be happening with the Veterans' Administration medical services? All supported this very strongly.

6. *Personnel positions.*—Should Congress deal with positions as a line item in the budget? Most would welcome this, but felt that Congress would be unwilling to undertake it. A few were concerned about rigidifying management in this way.

7. *Budget.*—Would forward funding be helpful in dealing with the budgetary uncertainties and instabilities? Almost all favored this change.

8. *The Cancer Institute.*—Should the extraordinary powers of the National Cancer Institute be modified? Almost all informants favored this change, including informants from the Cancer Institute itself.

9. *Minority Group Research Training.*—Should the statute be altered to allow pre-Baccalaureate support for research training for minority group members? All informants who had an opinion supported this change.

APPENDIX 1

Research Advances of the National Institutes of Health by Institute

Each institute of NIH was asked to submit a short summary of research advances during the past five years sponsored by that institute. This Appendix contains the responses of the ten institutes and the Division of Research Resources.

The National Institute of Aging, which was formed in 1974, was not asked to submit material.

The summaries are printed here as they were received from the institutes, and are in order of the establishment of the institute in time. The Division of Research Resources, which funds research centers and lets contracts, is included at the end.

NATIONAL CANCER INSTITUTE-SUPPORTED RESEARCH ACHIEVEMENTS, 1971–1975

Intramural

(a) Patterns of cancer occurrence are changing, probably as a result of environmental factors and individual behavior patterns, according to data from the Third National Cancer Survey, a study of seven metropolitan areas and two entire states that was made between 1969 and 1971 by Dr. Sidney J. Cutler and his associates at the National Cancer Institute. Results of the survey have revealed changes in trends by race, sex, and form of cancer when compared with previous surveys taken in 1939 and 1948. The comparisons are being evaluated to pinpoint possible contributing factors in cancer occurrence.

(b) Metabolism of the chemical, cyclic adenosine monophosphate (cyclic AMP), appears to be disrupted when laboratory-grown cells are made cancerous by infection with cancer-causing viruses. The amount of cyclic AMP in the cells diminishes. When cyclic AMP is added to these cancerous cells to make up the deficit, they regain some of the characteristics of normal cells. The cells revert to the typically malignant appearance when the addition of cyclic AMP is discontinued, reported Dr. Ira Pastan and his associates at the National Cancer Institute in a 1971 report in the *Proceedings of the National Academy of Sciences*. This study suggested that cyclic AMP may be associated with control of cell movement and growth, both of which become deranged when cells become cancerous.

(c) Development of a four-drug regimen for combination treatment of advanced Hodgkin's disease has dramatically improved chances for extended disease-free survival, according to a report by National Cancer Institute clinical investigators during a symposium on Hodgkin's diseases in October 1971. Studies of a combination of prednisone, procarbazine, vincristine and either nitrogen mustard or cyclophosphamide achieved a more than 50 percent survival for 4 to 7 years without evidence of disease.

(d) Preventive radiation treatment has raised the 5-year survival rate above 95 percent in patients with early diagnosed Hodgkin's disease, Dr. Ralph E. Johnson of the National Cancer Institute reported during a symposium on Hodgkin's disease in October 1971. A study of 164 patients over a 7-year period at NCI demonstrated that supervoltage X-irradiation to diagnosed disease sites plus prophylactic radiation to uninvolved areas with a high potential for disease extension greatly increased chances for disease-free five-year survival in patients with this type of cancer of the lymphatic system. The therapy also raised the 5-year survival to more than 75 percent in patients with more advanced Hodgkin's disease.

(e) National Cancer Institute scientists have developed a more efficient, rapid and economical way to screen chemicals for carcinogenic activity, by using hamster embryo cells exposed to test chemicals in the pregnant animal and then grown in tissue culture. With the new procedure, a test chemical is first injected into a pregnant hamster. The hamster embryos, exposed to both the chemical and its metabolic products, are later removed and the embryonic cells grown in a test tube. Cancerous transformation is detectable when the cells are viewed under a

microscope and confirmed by injecting the transformed cells into healthy hamsters where they produce cancers. The method may eventually replace the more costly and slower method of feeding possible carcinogenic substances to living laboratory animals and waiting, often for more than two years, to evaluate any effect. The new procedure, described in the June 1973 *Archives of Pathology* by NCI's Dr. Joseph A. DiPaolo and associates, can show deleterious effects of chemicals on the embryonal tissue culture cells in as little as two weeks.

(f) Cancer-causing viruses may act on the surface membranes of cells to change cell susceptibility to the body's immunological defense system, Dr. Peter T. Mora of the National Cancer Institute reported at the September 1974 meeting of the American Chemical Society. Dr. Mora and coworkers found that laboratory-grown mouse cancer cells lose a relatively small protein component from their surface membranes when infected with Simian Virus 40, a virus that causes cancer in hamsters but not in mice. The virus-infected cells also acquire new immunologic properties and become less capable of inducing tumors when implanted in mice. Dr. Moro speculated that the virus caused a change in the cells' membranes that made them more susceptible to normal immunological control.

(g) National Cancer Institute clinical investigators have achieved a complete disappearance of symptons of advanced, recurrent breast cancer in a small but significant proportion of patients with a four-drug combination of Cytoxan, methotrexate, 5-fluorouracil and prednisone. Dr. Vincent T. DeVita, Jr., reported at a 1974 symposium on cancer therapy that the drugs produced at least a partial response on 17 (68 percent) of 25 patients, including a complete remission in 7 (28 percent) of them. Those who responded to treatment had a median survival time of more than 15 months, compared with a median survival time of 6 months for the 8 patients who failed to respond. The drug combination has been the basis for cooperative clinical studies in larger numbers of advanced breast cancer patients, and for studies in which three of the drugs have been given after initial breast surgery to patients known to be at high risk of relapse.

(h) National Cancer Institute scientists have isolated a candidate human virus thought to be associated in some way with development of a form of leukemia. The virus isolation, reported by Drs. Robert C. Gallo and Robert E. Gallagher before the American Society of Hematology in December 1974, was successfully achieved from the laboratory-grown leukemic cells of a 61-year-old woman with acute myelogenous leukemia. Continuing studies are under way to determine whether the virus occurs in cells from other patients and other forms of leukemia. Other research is directed toward identifying a viral-related antigen that could lead to new therapies or diagnostic tests.

(i) Combination chemotherapy has improved the chances for disease-free survival and cure in patients with advanced diffuse histiocytic lymphoma, Dr. Vincent T. DeVita, Jr., and his associates at the National Cancer Institute reported in the February 1975 issue of *Lancet*. Ten of 27 patients with advanced disease achieved a complete disappearance of symptoms for two to nearly nine years after treatment with a four-drug combination called MOPP (Mustargen, Oncovin, procarbazine, and prednisone). Two-year disease-free remission represents cure of this particularly virulent form of lymphoma. Until development of the new therapeutic approach, advanced diffuse histiocytic lymphoma was thought to be invariably fatal.

(j) A new compilation of cancer death rates for each of the 3,056 counties in the 48 contiguous United States and the District of Columbia should provide clues for detailed investigations into occupational and other environmental factors in the causation of cancer. The National Cancer Institute study comprises an analysis of death certificates from the U.S. counties translated into age-adjusted mortality rates per 100,000 population for 35 types of cancer, and maps to illustrate and pinpoint above- and below-average rates for different locales. The county-by-county mortality data and accompanying book of maps were published in 1974 and 1975, respectively, by Dr. Thomas J. Mason and his associates in NCI's Epidemiology Branch.

Extramural

(a) A connection between use of the drug, diethylstilbestrol (DES), a synthetic hormone, and development of a rare type of genital cancer in female offspring has been shown by Dr. Arthur L. Herbst, a National Cancer Institute grantee at the Massachusetts General Hospital. Dr Herbst and his associates reported in the *New England Journal of Medicine* in 1971 that daughters of women who had taken DES during pregnancy sometimes developed a rare cancer called clear cell adenocarcinoma in the vaginal or cervical regions. These tumors appeared at an early age, after the onset of puberty. Other noncancerous genital

tract abnormalities also have been associated with exposure to the drug during pregnancy.

(b) A test to predict the response of advanced breast cancer to hormone therapy has been developed by Dr. Elwood V. Jensen of the Ben May Laboratory for Cancer Research, University of Chicago, with support from the National Cancer Institute. Dr. Jensen and his associates reported in a 1971 National Cancer Institute Monograph that the difference in a level of a hormone-binding protein called estrogen receptor, found in a breast cancer patient's tissues usually correlated with their response to hormone therapy. This test can aid clinicians in selecting modes of therapy without resorting to trial and error.

(c) Drs. John Frost and Bernard Marsh of the Johns Hopkins University, Baltimore, reported at a 1972 National Cancer Institute symposium on lung cancer the ability to detect lung cancer by the examination of cells obtained from deep cough sputum samples, combined with scanning of lung passages with a flexible fiberoptic bronchoscope. With support from NCI, the scientists developed techniques for obtaining cancer cells from within the lungs and using the bronchoscope to locate their site of origin. The Johns Hopkins physicians and others, including Dr. Robert Fontana of the Mayo Clinic, currently are using the techniques to determine if lung cancer can be detected early enough to improve the outcome of treatment.

(d) The combination of physical examination and X-ray mammography in breast cancer screening has been shown to decrease breast cancer deaths by one-third over a five-year follow-up period, in an NCI-supported study conducted by the Health Insurance Plan of Greater New York. In the March 1973 issue of the *American Journal of Roentgenology, Radiation Therapy and Nuclear Medicine*, Dr. Philip Strax and colleagues reported on findings of the study of 31,000 women screened annually for breast cancer, compared with 31,000 women given their usual comprehensive medical care. One-third (44 of 132) of the breast cancers detected in the screening program were found by X-ray mammography before the tumors were large enough to be detected physically. This early detection, while the tumors are more readily treatable and curable, has been given credit for the lower death rate.

(e) The first synthesis of an artificial and potentially functioning gene, the nucleic acid combinations that control heredity, was announced by National Cancer Institute grantee, Dr. H. Gobind Khorana, of the Massachusetts Institute of Technology at a scientific meeting in August 1973. His research group painstakingly pieced together a chain of 126 units of deoxyribonucleic acid (DNA) to form the gene. The particular gene synthesized may direct the formation of a molecule of ribonuclic acid (RNA) that is responsible for incorporating a specific amino acid, tyrosine, into the protein-building process. Further investigations, made possible by the gene synthesis, will concern the gene's regulatory mechanism and eventually control of cell growth and multiplication.

(f) Anticancer drugs have been used effectively, after initial surgery, to delay and perhaps prevent recurrence of osteogenic sarcoma, a virulent form of bone cancer, in patients treated by investigators in NCI-supported studies at several institutions. Scientists reported at a research meeting in March 1974 that patients had remained free of disease for periods approaching two years after surgery and treatment with Adriamycin or high doses of methotrexate combined with citrovorum factor to "rescue" the patients from methotrexate's side effects. Without drug treatment, most patients with osteogenic sarcoma relapse within a year after surgery.

(g) Wilms' tumor, a kidney tumor of childhood, has responded to combined treatment modalities including surgery, radiotherapy, and two anticancer drugs, actinomycin D and vincristine. Although each case is different, depending on whether there is obvious metastatic spread, the combination of surgery, radiation and the two drugs used in a study conducted by the NCI-supported National Wilms' Tumor Study Group has improved the chances of killing all the cancer cells. Dr. Giulio J. D'Angio, chairman of the group, reported at a meeting in May 1974 that the combined therapy had achieved a 2-year survival rate of about 80 percent in a group of 196 patients. In early stages of the disease, the 2-year survival rate approached 100 percent. Wilms' tumor is one of the more common childhood malignancies, and the three modality treatment combination has greatly improved the survival rate over that experienced with only one or two of the treatment regimens.

(h) Adriamycin, a new anticancer drug developed in Italy, has shown great promise in treating various types of cancer during National Cancer Institute-supported trials. The drug has shown activity alone and in combination with other

treatment modalities against cancers of connective tissue, advanced breast cancer, lung cancer, lymphomas, acute leukemias, childhood cancers, and cancers of the ovary, bladder and thyroid. Adriamycin was approved as a prescription drug for use in cancer patients by the Food and Drug Administration in August 1974.

(i) The rate of recurrence of breast cancer has been reduced significantly in preliminary trials in patients treated after surgery with a single anticancer drug, L-phenylalanine mustard (L-PAM), in an NCI-supported study. Dr. Bernard Fisher, chairman of the National Surgical Adjuvant Breast Project cooperative group, reported at a meeting sponsored by the NCI Breast Cancer Task Force in September 1974 that cancer had recurred after 2 years in only 1 of 30 patients receiving L-PAM, compared with 11 recurrences among 37 patients receiving surgery but no drug. The patients were premenopausal women who had been found upon surgery to have spread of cancer cells to axillary (armpit) lymph nodes, indicating a high risk of relapse. The patients are under follow-up study to assess the long-term effects.

(j) More than 50 percent of children suffering from acute lymphocytic leukemia were alive and without evidence of disease more than five years after starting treatment with a combination of anticancer drugs and radiation in a study at St. Jude Children's Research Hospital in Memphis, Dr. Joseph V. Simone, a National Cancer Institute grantee, reported at a 1974 symposium on cancer therapy. Before discovery of anticancer drugs, most children with the disease died within months. The combination of anticancer drugs with radiation that kills hidden leukemia cells that migrate to the brain has dramatically improved the outlook for victims of childhood leukemia.

Significant Research Advances, National Heart, Lung, and Blood Institute, 1970–75

INTRAMURAL RESEARCH

Nitroglycerin for Acute Heart Attacks

Nitroglycerin, the accepted treatment for angina pectoris, was found to reduce the extent and severity of heart-muscle damage resulting from blood deprivation (ischemia) and to help protect the heart against arrhythmias when given very soon after acute heart attacks.

The extent and severity of heart-muscle damage resulting from a heart attack is often a crucial factor affecting survival and the amount of residual disability after recovery. Arrhythmias remain a significant cause of death during the critical phase after acute heart attacks. Herein lies the potential importance of clinical studies that may define a new application for one of the oldest cardiac drugs.

Kallikrein-Kinin System in Hypertension

Clinically significant evidence has been developed on the kallikrein-kinin system which indicates it plays an important role in the regulation of blood pressure and blood flow and in the handling of salt and water balance in the kidney. Studies have shown that urinary kallikrein levels tend to be similar in members of the same family and to be inversely proportional to blood pressure levels. Excretion is abnormally high in patients with excessive aldosterone production due to tumors or other pathological conditions affecting the adrenal glands which in turn may raise blood pressure by promoting salt and fluid retention and increase in blood volume. This determination provides a means to distinguish between this form of secondary hypertension and essential hypertension, the cause of which remains obscure. Kallikrein excretion is stimulated or depressed by the same stimuli which affect aldosterone secretion. It was these observations that suggest the kallikrein-kinin system may be intimately involved in renal mechanisms governing fluid and electrolyte balance as well as those regulating blood pressure.

Other clinically significant observations are that kallikrein levels are very low or undetectable in urine collected from the blood-deprived or blocked kidney, thus low urinary kallikrein levels is a valuable indicator in selecting patients whose renal hypertension is likely to be cured or improved by surgery. It has been noted that plasma levels of kallikrein are lower in women on oral contraceptives than on those not taking the pill, which is of clinical interest in view of the increased incidence of hypertension reported among pill users.

Research on Cooley's Anemia (Beta Thalassemia)

Cooley's anemia, also called beta thalassemia, is a serious hereditary hemoglobin disorder that affects chiefly Greeks, Italians, and other Mediterranean peoples and their descendants. The thalassemias comprise a family of diseases whose

prevalence in the U.S. is not known with certainty, but worldwide, these genetic defects are very common and the severe forms of the thalassemias are a major health problem.

Earlier NHLI studies disclosed the genetic defect underlying Cooley's anemia which leads to "crippling" the red blood cell and causing it to be destroyed long before it has lived out its normal life span. This is the basis of the anemia that can now be corrected only by periodic transfusions.

Following a detailed description of the mechanisms of this disease, NHLI scientists have developed a technique to study the basic mechanism of the hereditary blood disorders, cell-fusion. The cell fusion technique has effectively isolated human chromosomes to study what genes a specific chromosome, or how the genetic blueprints carried by the DNA of the genes are translated (via RNA) into structural proteins, enzymes, and other substances produced in the cell.

Since the basic flaw in Cooley's anemia appears to be faulty regulation in the synthesis of a gene product, cell-fusion techniques offer a promising means of zeroing in on mechanisms which may affect hemoglobin synthesis in the circulating red blood cell.

Continued research on the genetic flaw in Cooley's anemia may lead, in time, to methods of treatment both more direct and more effective than periodic transfusions of whole blood or packed red cells to replace those destroyed as a result of the disease and to provide a model for study of all the hereditary blood diseases.

Drug Metabolism and Drug Toxicity

The metabolism of otherwise beneficial drugs may result in the formation of oxic compounds that damage the liver even as it acts on the parent drug, or that injure the kidneys even as they are concentrating the drug metabolites prior to excretion. NHLI studies have shown that the anti-TB drug *Isoniazid* and the antidepressant *Iproniazid* provide such metabolites. Though highly effective and relatively nontoxic in most patients, these drugs cause serious liver damage in others.

NHLI studies showed that the metabolism of isoniazid involved a chemical reaction called acetylation. The rate of acetylation varied from one pateint to another, but was nearly always faster in Orientals than in patients of other races. Thus, an unusually high percentage of patients afflicted with isoniazid liver injury were Orientals.

NHLI studies have indicated that alpha-methyl DOPA, a drug widely prescribed for the treatment of moderate to severe hypertension produces severe liver damage in a small percentage of patients. In as many as 15 percent of all patients taking it, the drug produces some evidence of liver dysfunction even though it may not produce overt clinical symptoms.

Echocardiography in Cardiovascular Diagnosis

NHLI studies show that echocardiography is a painless, safe, noninvasive technique for visualizing the heart and great vessels by means of reflected ultrasound. It is proving to be extremely useful in the diagnosis and evaluation of a variety of congential and acquired heart conditions.

A scanner placed on the patient's chest directs an ultrasound beam through the intact chest wall at the section of the heart to be examined. Like X-rays, ultrasound passes readily through bodily tissues and fluids; but a portion of the beam is reflected from the surface of the heart and from the blood-tissue interfaces within it. The returning echoes are converted into a cross-sectional image of the heart, permitting detection of structural defects and assessment of their effects on heart performance.

Echocardiography is highly effective in diagnosing transposition of the great vessels, tetralogy of Fallor, absence of a ventricular spetum, and other congenital heart conditions. It often provides information on those conditions that cannot be obtained by conventional X-ray visualization techniques (angiography) and may even obviate the need for angiography, a procedure not without hazard in critically ill infants.

Echocardiography is also uniquely valuable in the diagnosis of asymmetrical septal hypertrophy (ASH), a genetically transmitted disease of heart muscle. Studies now in progress indicate that ASH may become clinically manifest in infancy, may be a factor in sudden infant death, or may lead to heart failure and death in the early months of life. It seems likely that ASH may be more common than generally supposed, since non-obstructive ASH if often difficult to detect by techniques other than echocardiography, whose potential in cardiovascular diagnosis is only beginning to be realized.

Heart Valve Replacement

The replacement of diseased heart valves with artificial substitutes has restored health to thousands of victims of rheumatic heart disease. Although most patients do well after valve replacement, others show little improvement despite adequate valve function and their prospects for long-term survival are relatively poor.

In patients requiring mitral or tricuspid valve replacement for rheumatic heart disease, but whose left ventricles are of normal size, heart valves from pigs appear to outperform artificial disc valves on two counts; lower mortality rates during the first six months after surgery and freedom from thomboembolic complications of valve replacement.

In the NHLI studies, Reis-Hancock porcine valves, mounted on prosthetic frames for ease of insertion, were compared with two types of disc valves in 74 patients undergoing mitral valve replacement and 14 others undergoing combined mitral and tricuspid replacement. Among patients receiving xenograft valves, mortality rates within six months after operation were less than half those occurring among disc-valve recipients. During this period, approximately 30 percent of patients receiving the artificial valves developed clotting complications despite maintenance on anticoagulant drugs. None occurred in the xenograft recipients, who received no anticoagulants postoperatively.

Respiratory Failure and Respiratory Assistance

NHLI scientists have developed a spiral-coil membrane oxygenator with a very thin membrane without the pinhole defects that have been the chief cause of membrane failure in oxygenators. Methods were developed to permit casting flawless silicone rubber membranes less than one thousandth of an inch thick needed by the new oxygenator.

NHLI scientists have also developed a technique for obtaining measurements of blood levels of both oxygen and carbon dioxide without repeated withdrawal of blood. Prolonged use of blood oxygenators and other forms of intensive respiratory care for victims of acute respiratory failure or other respiratory crises require such measurements frequently. The device is now undergoing laboratory testing and may prove to be of great value in the physiological monitoring of patients in intensive care units.

NHLI scientists in collaboration with scientists in Italy have developed new instrumentation for the study of red blood cells which for the first time gives the ability to measure the oxygen carrying capacity of intact red blood cells. This instrumentation is being used in clinical studies of sickle cell anemia. The data provided by this instrumentation frequently is of greater clinical value than determination of blood oxygen levels because it provides an index of the actual amount of oxygen available to the tissues, hence is highly useful in assessing the clinical status of patients in respiratory failure, evaluating effect of sickle cell crisis or other hemoglobin disorders and the effectiveness of therapeutic procedures.

Research on Growth Hormone

NHLI scientists have developed a cell culture technique which promises to increase the supply of growth hormone available for clinical and research purposes. Growth hormone is important in disorders characterized by growth retardation. It may also be involved in anabolic processes in general, such as the repair of heart muscle damage after acute heart attacks. Until now only miniscule amounts of the hormone (obtained from cadavers) have been available for therapeutic purposes.

Lipid-Lowering Drugs

A factor strongly and consistently associated with increased susceptibility to premature coronary heart disease is elevated blood levels of cholestrol and other fatty substances, collectively called lipids.

The blood-lipid abnormality may often be improved by switching to a diet in which cholesterol and total fat are reduced and unsaturated fats are substituted for part of the saturated fats.

During recent years, research done at the NHLI and elsewhere has also established that elevated blood lipids may be indicative of one or another of five distinct lipid-transport disorders, designated as hyperlipoproteinemias Types I through V. Each type differs from the others in its clinical manifestations, risk for the patient, and responsiveness to therapy. These disorders may be diagnosed, sometimes from infancy and almost invariably by age 40, through blood lipoprotein analysis or other simpler techniques. Therapeutic diets have been devised for each type, and used alone or supplemented (if necessary) with specific lipid-lowering drugs, they can completely correct or substantially improve the blood lipid abnormality in nearly all cases.

Neural Code

The NHLI scientist who "cracked" the genetic code has made the first major step toward cracking the neural code. Significant progress has been made in growing brain cells in tissue culture which provides the means to study the neural code.

EXTRAMURAL RESEARCH

Reduction of Heart-Attack Damage

Research supported by the National Heart and Lung Institute has yielded several promising methods for reducing the extent and severity of heart-muscle damage resulting from acute heart attacks.

Animal studies by several research teams, indicate that drugs called beta adrenergic blocking agents reduce the extent of ischemic injury after inducted heart attacks. Other grantees have found that the enzyme hyaluronidase dramatically decreases heart-muscle damage occurring soon after acute heart attacks. Others have findings which indicate the drug mannitol also decreases infarct size. It also improves heart-muscle contractility by increasing calcium availability. Certain steroids may reduce heart-muscle damage after heart attacks, apparently by reducing inflammation and slowing the breakdown of tissues in ischemic areas. Several research teams report that a circulatory-assist technique called balloon pumping reduces infarct size after an acute heart attack. The combination of increased coronary perfusion and reduced heart work appears responsible for an observed reduction of permanent heart-muscle damage.

These studies indicate that the usual destructive effects of acute heart attacks on the heart muscle can be minimized by timely and appropriate clinical interventions. They also suggest that a more aggressive approach based on sound physiological and clinical principles might save many lives and restore many persons who would otherwise be permanently disabled to a normal existence.

Bone Scanning Agent Reveals Infarcts

Now that it is becoming possible for cardiologists and heart surgeons to save heart muscle stricken by coronary occlusive disease, there is an urgent need for better ways of visualizing the injured myocardial areas.

NHLI grantee scientists have reported a tendency of calcium to concentrate in damaged myocardial cells, and that agents in common clinical use for bone scanning have a particular affinity for calcium. From this observation a simple, non-invasive, safe, and inexpensive technique has been developed to chart the areas of acute myocardial infarction. This provides a valuable tool not only for establishing the presence or absence of acute infarction, but for estimating the size of the area damaged by it and hopefully the effect of various therapeutic measures on the size and progression of myocardial infarcts.

Continuous Positive Airway Pressure in "Hyaline Membrance Disease"

Continuous positive airway pressure (CPAP) as a treatment for respiratory distress in newborn children now yields survival rates in the range of 90 percent, a figure unimaginable 10 years ago. This amounts to a clear therapeutic breakthrough against this leading cause of neonatal death.

"Hyaline membrane disease" is regarded as a condition of lung immaturity and largely an affliction of the prematurely born. This respiratory distress syndrome affects about 40,000 newborns in the U.S. each year and, until recently, killed more than half of these.

The idea of keeping the airways of these infants under continuous positive pressure originated with a grantee and his associates at the University of California School of Medicine in San Francisco supported by NHLI, NIGMS and NICHD.

Biocompatible Materials and Cardiovascular Prostheses

Significant advances have been made by NHLI contractors and grantees in the development of biocompatible materials for use in blood oxygenators, heart-assist devices, artificial heart valves, and other cardiovascular prostheses.

Hydrogels, a class of gelatinous compounds with excellent blood compatibility but lacking mechanical strength and toughness have been bonded over the surfaces of a number of polymers, excellent in many respects for prostheses but which, unlocated are incompatibile with blood after prolonged contact. The result has been a group of the most promising materials yet developed for the fabrication of certain prostheses.

Artificial blood vessels with mechanical properties similar to living tissue have been fabricated. Among their advantages are resistance to buckling or kinking when flexed and normal response to blood pressure changes in propagating pressure pulse waves generated by the heart. Similar materials may find application in artificial heart valves and other prostheses.

Apoprotein Structure and Function

Following the determination of the amino-acid sequence of the first recognized apoprotein or natural "detergent" of the bloodstream (so called because of the property of combining with lipids—cholesterol, triglyceride, and phospholipid—to render them soluble in blood) by an NHLI Intramural scientist in 1971 much of the chain structure of the other five previous apoproteins have been described. Until recently, however, there was no understanding as to how apoproteins combine with lipids.

An NHLI grantee, formerly with the NHLI Intramural program has now provided a plausible explanation of how some apoproteins combine with phopsholipid. His work has led to a new view of the apoprotein molecule as a unique, two faced or *amphipathic* helical structure in which a large non-polar face bends with the fatty acid chains of phospholipids, and a polar face that combines with water-soluble portions of phospholipid. Computer searches of existing structural data enabled the constructions of molecular models of three different apoproteins in which the arrangement of amphipathic regions and charged groups were consistent with the new theory. Such knowledge enhances the probability of using the "detergent" quality of the apoprotein in a bodily defense against atherosclerosis.

Molecular Basis for Familial Hypercholesterolemia

A related research effort concerning elevated blood lipids has further extended understanding of one of the five forms of lipid-transport disorders known collectively as hyperlipoproteinemia.

Though an important source of cholesterol is dietary intake, the principal producer of the circulating cholesterol in human blood plasma is the liver which forms what is known as very low density lipoprotein (VLDL).

Increased plasma level of LDL characterizes Type II hyperlipoproteinemia. This disorder may occur as the result of a secondary cause, such as hypothyroidism, but often it is the result of a primary, genetically determined abnormality. Previous studies of primary familial Type II hyperlipoproteinemia, or as it is also known, famlial hypercholesterolemia, strongly suggest that it is inherited as a dominant genetic trait, much as brown eyes are dominant over blue eyes.

Familial Type II hyperlipoproteinemia may in fact be one of the most common genetically determined abnormalities and is an important subject of study because of its involvement in increased risk of coronary heart disease (CHD).

It was demonstrated in the NHLI laboratories in Bethesda a few years ago that the increased levels of LDL in the blood of Type II patients resulted from a decrease in LDL clearance or removal from the bloodstream. In research funded by the NHLI, a grantee observed that many body cells, including those of the skin, possess the ability to act as "miniature livers" in metabolizing fat and that there is a dominant genetic mode of transmission for this disorder.

These findings should prove of worth, both by contributing to the understanding of a common and important human disorder, and by providing a new laboratory system for studying genetic phenomena.

Enzyme Isolation Advance Against Emphysema

A National Heart and Lung Institute grant-aided team of biochemists isolated, in pure form, the enzyme antitrypsin (alpha-1-antitrypsin).

Their accomplishment—the availability of a purified antitrypsin—may be the key to defining the physico-chemical structure and normal function of this enzyme, and aid in understanding how severe, hereditary deficiencies of antitrypsin interact with enviromental factors to produce a particularly severe kind of emphysemsa. Moreover, application of the biochemical isolation procedures to the more than 20 known variant forms of antitrypsin is likely to lead to delineation of structural and functional differences among them, and to an understanding of how enzyme deficiency states, involving one or more of these variant enzymes, can lead to disease.

The fact that at least some forms of antitrypsin deficiency can apparently interact with environmental factors (smoking, dust inhalation, and other forms of air pollution) to cause emphysema has led to the theory that one or more of the proteases (protein-dissolving enzymes normally inhibited by antitrypsin in the lung) are responsible for the lung damage in this kind of emphysema.

Certainly the availability of purified antitrypsin will greatly enhance further attempts to define protease inhibition and other functions of antitrypsin, including studies of its biosynthesis, transport, sites and mechanisms of action, and breakdown within the body.

Surfactant-Producing Cells Available for Study

The problem of respiratory distress in the newborn is rooted in their lack of a pulmonary surfactant necessary for normal lung expansion. NHLI grantees have developed a method of lung cell isolation that makes homogenous populations of granular pneumocytes available for the first time. This advance is important because the granular pneumocyte—one of more than forty different types of lung cells—is the source of the surfactant missing in these babies. Isolation of a homogenous cell population is a first step toward understanding the complex events in pulmonary biology.

The respiratory distress syndrome still accounts for the largest portion of infants who die in our nurseries. It is already clear that the study and biochemical manipulation of granular pneumocyte metabolism can help explain why these babies lack surfactant, and can also provide clinically useful ways of stimulating its development in infants with the syndrome.

Heart-Assist Device

One of the most promising devices for providing temporary pumping assistance to heavily damaged, failing hearts is the left ventricular assist device (LVAD), developed with NHLI research-contract funds.

Of several LVAD models developed to date, models VII and X have performed well during extensive laboratory and animal tests, and are undergoing preliminary clinical trials.

The pump can handle any fraction or all of the blood normally pumped by the left ventricle, thereby maintaining an adequate blood pressure while substantially reducing the workload and energy expenditure of the heart. This "breather" may enable a heavily damaged heart to mend its damage and gradually resume its circulatory duties. The patient would then be "weaned" from the device and the device removed.

Regression of Atherosclerotic

Recent experimental studies by NHLI grant-aided scientists have yielded evidence of *regression* of atherosclerotic lesions. Laboratory animals were fed a diet rich in fat and cholesterol over a period of 17 months. Following evidence that this feeding had produced atheromatous plaques, the remaining animals were removed from the atherogenic diet and placed on either of two cholesterol-free "regression diets." At the end of this period, autopsy studies demonstrated that overall coronary narrowing had been reduced in severity to 18 and 22 percent respectively in these animals, and this was accompanied by the observation of fewer plaques elsewhere in the arterial tree.

National Institute of Allergy and Infectious Diseases

Significant Scientific Accomplishments 1970–1975

Introduction

A time phased list of scientific accomplishments invites controversy—not dispute over whether the item is important or not but rather as to whether an *individual* should be credited and *when* the accomplishment was achieved. One of the few kinds of scientific achievement that a single investigator might clearly claim as exclusive discovery is the isolation and identification of a new virus or bacterium. Most scientific advances borrow so heavily from the concepts, the techniques, and the work of others that an attempt to claim exclusive credit is largely fiction. Whatever his pardonable pride in his achievements, the scientist himself acknowledges his debt to others by his bibliography which is such an essential part of any report in a professional journal.

Similarly the citation of a date more truly represents the year when the fuller import of a long chain of scientific observations was generally recognized then it does the precise date of discovery.

Significant Scientific Accomplishments by Extramural Researchers

Development of a purfied gonococcal component (pili) as the reagent for a specific blood test for gonorrheae, (1974). A major problem in the control of gonorrheae is the difficulty of easily and quickly diagnosing the disease especially

in patients who have no symptoms but are an important source of infection for others. Non invasive tests of this sort appear to be an answer.

Analysis of the antigenic components of influenza virus—their inheritance and role in protection against disease, (1973). Development of laboratory produced hybrid strains of influenza virus for use in improved influenza vaccines.

Transplantation of unrelated genes, (1974). Many of these experiments have involved the insertion or substitution of gene material from one form of life to another easily reproduced form such as bacteria. Success in this "hybridization" has been achieved between forms as diverse as toads and bacteria. The possibilities for good or evil seem enormously important both commercially and medically.

Combined rational drug therapy for deep seated fungal infections, (1975). Fungal infections of the deep seated body organs have always been difficult to treat. Many of the patients are debilitated or immunosuppressed and the drugs such as amphotericin B are relatively toxic. Combined therapy can show enhanced action—one drug such as amphotericin apparently making "holes" in fungal cell membranes allowing another drug, such as rifampin, to enter and interfere with another important fungal process such as synthesis of genetic material (RNA).

Recognition of the relationship between transplantation (histocompatability) or associated antigens and the relative susceptibility to a variety of infections, "inherited" and metabolic diseases.

Development of radio-immune assays for the precise and specific measurement of small quantities of a wide variety of hormones and other clinically or diagnostically important substances.

Development of the theoretical concepts and the techniques for laboratory exploration of the ways in which viruses invade cells, mix their genetic material with that of host cells and thereby influence, possibly only after a long period of time, the manifestation of disease.

SIGNIFICANT SCIENTIFIC ACCOMPLISHMENTS BY DIRECT OPERATIONS

Direct operations includes the Collaborative (Contracts) Research and the Laboratory and Clinical Research Programs.

Hepatitis type B vaccines protection of chimpanzees against challenge, (1975). The demonstration of the efficacy of this prototype vaccine in an animal model system is an obvious important step in the development of a human vaccine.

Specific identification of an infant diarrhea virus, (1975). Immuno-electron microscopy was used to visualize and specifically identify a new virus responsible for a significant amount of infant diarrhea. Even in developed countries such as the United States this disease causes 5 to 10% infant deaths.

Preparation and field testing of polyvalent pneumococcal vaccines, (1975). Influenza and pneumonia combined account for 60,000 to 65,000 deaths annually in the U.S., the 4th highest cause of death from disease. In spite of antibiotics, a large percentage of these deaths are still due to pneumococcal pneumonia. Additionally, pneumococcal middle ear infection (otitis media) is a painful recurrent disease that frequently results in some degree of permanent loss and consequent learning or personality problems. Whether vaccine is a feasible means of preventing otitis media is just being tested.

Preparation and field testing of a purified bacterial component (polysaccharide) vaccine against meningitis, (1974).

Detection and specific identification of the virus causing hepatitis type A by immuno-electron microscopy, (1974). Although the viral etiology of hepatitis type A has been suspected for many years it could not be proven nor was any specific diagnostic test available.

Development of attenuated mutants for use in vaccines against influenza and other viral respiratory diseases, (1973).

Demonstration of the effectiveness of clindamycin-quinine therapy for drug-resistant falciparum malaria. Malaria is a major cause of death world-wide and the parasite is showing increasing resistance to the excellent chemotherapeutic agents developed during World War II. The importance of alternate forms of therapy, particularly as DDT resistance of the mosquito vector is also increasing, cannot be overestimated.

Discovery of sexuality (+ and − mating types) in two species of pathogenic fungi and the probable relation of sexual type to human infections.

Discovery of a method for identifying the origin of malignant cells, (1975). Certain types of cancer including leukemia may arise from either of 3 main types of white blood cells. A laboratory method for studying the mature cancer cell now permits the origin of the cancer cell to be determined. The availability of

this technique is expected to lead to improvements in diagnosis, specifically tailored therapy and certainly to improved understanding of the process by which cancer develops.

Elucidation of the mechanism of action of the natural antiviral substance—interferon—and development of methods for inducing it with chemicals. Viral infection causes the body cells to produce a specific substance—interferon—which appears to be one of the main mechanisms used to rid the body of viral infection. The potential clinical application of interferon in antiviral and antitumor therapy and chemical ways of inducing interferron in tissues are being explored.

NATIONAL INSTITUTE OF DENTAL RESEARCH

EXTRAMURAL RESEARCH ADVANCES 1976

The HLA cell surface antigens have been shown to be abnormally inherited in some instances of human cleft palate.

The new finding that facial bony sutures fuse much later than previously believed makes it feasible to treat patients with orthodontic disfigurements well into adulthood.

Experimental induction of cleft palate in primates was achieved in bonnet monkeys by investigators using high doses of triamcinolone acetonide.

Evidence has been obtained that maternal genetic factors related to the H-2 histocompatibility gene loci affect the susceptibility of mouse embryos to cleft lip/palate.

Researchers have isolated specific groups of anaerobic Gram-negative bacteria from individuals with the severe periodontal condition called peridontosis and subsequently showed that these organisms cause severe periodontal bone loss in gnotobiotic animals.

Free-standing, unsplinted artificial teeth made of titanium in a cylindrical shape have been maintained (with crowns in functional occlusion) in the jawbones of baboons for up to 29 months.

Pathogenic strains of a Gram-positive filamentous human periodontal organism contain intracellular plasmids and synthesize an extracellular polysaccharide virulence factor, whereas non-pathogenic strains of the same organism do not contain plasmids and do not make the virulence factor.

Evidence has been obtained that the bone resorptive factor demonstrated to be present in the gingiva of man, monkey and the rat is a prostaglandin.

Osteoclast-Activating Factor from human lymphocytes, thought to play a role in the bone loss associated with periodontal disease, has been shown to cause local bone resorption not only in tissue culture, but also in animals.

Tissue culture studies have shown that osteoarthritis cartilage cells synthesize skin-type collagen rather than the cartilage-type collagen.

Intramural Research Advances 1976

Pilot projects have shown that, in communities where there is too little fluoride in the water, school children who rinse their mouths once a week with a dilute fluoride solution have about 40 percent less tooth decay than others in the same communities who do not. Therefore this year the NIDR is funding three-year demonstrations through 16 collaborative projects widely distributed over the U.S. in order to introduce this safe, simple, and cost-effective technique to the American public.

Differences in the composition of drinking water other than the amount of fluoride may explain contrasting levels of tooth decay in two isolated villages in Colombia, South America.

Unlike blood, which contains many immune globulins that help to protect the body against foreign proteins and bacteria, saliva contains chiefly the A type (IgA) of immune globulin which does not kill bacteria but does seem to prevent their adhesion. The discovery this year that the minor salivary glands contain much higher concentrations of IgA than the large parotid glands suggests that these numerous small glands may be the chief contributors to the supply of this globulin in saliva.

There has been some research which strongly suggests that infants get their first bacteria from their mothers. In the case of *Streptococcus mutans*, a bacterium strongly associated with tooth decay, the mode of transmission has been puzzling because it is not easy to implant in humans, and is very selective in its colonization sites. It may be found on one tooth and not on the next in the same mouth week after week. Recently a group of infants from a few weeks to about a year and a half in age were studied to try to establish when the *S. mutans* appeared and if

possible from what source. The investigators found it was not retrievable from babies before their teeth erupted except in two instances of infants who constantly wore a hard plastic appliance to bridge a cleft palate. Apparently this organism needs a hard surface on which to attach. The most common type of the organism could come from a variety of human sources, but the fact that one mother had the rare type b, and her infant also became infected with that type after its teeth erupted, is strong evidence that this organism is transmitted from mothers to their infants, because its only known source is from humans and a few animals closely associated with humans.

In an approach to finding a vaccine against tooth decay, monkeys were injected in the parotid gland ducts with an enzyme used by *S. mutans* in making sticky glucans from table sugar. The glucans enable it to attach to teeth and contribute to the film of plaque in which other acid-forming bacteria become trapped on teeth. The levels of serum and salivary antibodies (IgA immune globulins) were studied. Efforts to infect the animals with *S. mutans* later were made. The vaccine appeared to increase the IgA levels sufficiently to prevent the bacteria from attaching to a considerable extent.

There is evidence that fluoride not only makes enamel more resistant to acids, but directly inhibits bacterial reactions in plaque. Apparently it is the free fluorine ion slowly released into solution from salt compounds such as acid phosphate fluoride (APF) that are effective. Studies of the effects of APF gel on the ratio of *S. mutans* and *S. sanguis*, two common mouth bacteria, indicate that *S. mutans*, a prime suspect in tooth decay, is reduced in numbers by such treatment in plaque removed from chewing surfaces and between adjacent teeth. In the laboratory, such fluorides also lower the surface energy and decrease the wettability of the mineral component of enamel. This should make it harder for *S. mutans* to stick on tooth surfaces.

The first visible sign of tooth decay is usually a white spot in the enamel. When this can be seen, the enamel has already been considerably undermined by acid. There is a great need for some method to detect decay much earlier, particularly for surveys of large numbers of children's teeth. Now, a fluorescent dye mixed with a substance that readily penetrates very small (capillary) spaces may allow scientists to identify incipient decayed spots and to shorten clinical trials by a year.

Hopes that substituting other sugars for table sugar will substantially reduce tooth decay are now dim. Plaque forms even when food is fed by stomach tube, and mouth bacteria converts most sugars into acids as easily as they do table sugar (sucrose).

Mice were immunized against both types of herpes simplex virus to see if it would be possible to prevent the persistent infections of local nerve ganglia that often follow inoculation of surface tissues with this virus. Immunization protected many mice against nerve infections from the type 1 (fever blister) but not from the type 2 (genital) form of the virus.

A number of physicians have suspected that human diabetes, in some cases, may follow viral infections, and some forms of diabetes seem to run in families. Recent studies with mice show that certain strains are much more susceptible to diabetes resulting from infections with the encephalomyocarditis virus. In these mice, the virus destroys the beta cells in pancreatic islets of Langerhans, and the resultant interference with carbohydrate metabolism is very similar to that found in human diabetes. Therefore it seems possible that human diabetes may sometimes be related to a genetic susceptibility to viral infections.

Studies of periodontal disease, in which inflammation of the gums leads slowly to loss of tooth-supporting tissues and finally causes sound teeth to fall out, have shown that immune responses to bacterial products can cause local inflammation of these tissues. The immune system has two principal types of cells that control inflammatory reactions. One is derived from the thymus (T-cells) and is the originator of antibody manufacture. The other cell type comes from the bone marrow (B-cells). These white blood cells have chemicals on their cell walls which are now known to bind with special types of rather large molecules. When this happens, the B-cells are said to be activated. and will produce other biologically active substances called lymphokines that also cause inflammation and tissue destruction. So both parts of the immune system, if overstimulated, can damage rather than protect the body.

The step from inflammation to actual destruction (resorption) of bone begins to be a little clearer to see after considering information from two diseases. When lymph cells from patients with bone and lymph types of cancer are cultured, the culture fluid contains substances that destroy bone. Also inflamed tissues of

patients with rheumatoid arthritis and severe periodontal disease contain a collagenase enzyme that destroys bone. These two conditions suggest different ways of damaging the bone that underlies the teeth now that it is known that T- and B-lymph cells can both attract scavenger cells (macrophages) to the spot where they were activated, and can then interact with these macrophages in at least two ways. Macrophages, when stimulated by lymphocytes, can release collagenase. Macrophages also cooperate with lymphocytes to release another substance that signals special cells called osteoclasts to destroy bone. In this way the first immune responses of T- and B-cells which cause inflammation, could progress to secondary, more severe reactions that destroy bone faster than it can regenerate.

The National Caries Program, National Institute of Dentral Research, is initiating a fluoride mouthrinse demonstration program in 16 communities in over nine geographic regions on July 1. It is anticipated that approximately 40 to 60 thousand children in 8 to 10 thousand classrooms will be enrolled in the program. The 0.2% neutral sodium fluoride rinse was selected as the first preventive agent for demonstration because of its safety, low cost, and ease of implementation. Clinical trails utilizing the 0.2% neutral sodium fluoride mouthrinse have shown that the number of newly decayed teeth has been reduced by 20 to 50%. The demonstration of preventive measures is viewed by the National Caries Program as an integral step to convey clinical research findings to the private practice or community sector.

National Institute of Neurological and Communicative Disorders and Stroke

1. Mr. Michel. Dr. Tower, certainly in its 25 years of existence, what is now the National Institute of Neurological and Communicative Disorders and Stroke, has contributed greatly to the research efforts in this area and I would laud the Institute on its accomplishments. If we might, could you give us a little "sneak preview" of what your forthcoming anniversary publication will highlight? What do you feel has been the major breakthrough in neurological and communicative research over the past 25 years?

Dr. Tower. Thank you, Mr. Michel. We are grateful for the compliment you pay our Institute. Our Anniversary Publication is intended to span the entire field of neurosciences in which the Institute has been interested during the past 25 years. More than 180 leading authorities in the basic and clinical neurosciences and communicative sciences have contributed chapters on topics ranging from neuropharmacology and neuroimmunology to medical treatment of epilepsy and Parkinson's disease to diagnostic audiology and acquired congenital hearing defects, to name just a few. It will highlight research advances and predict future directions research may take.

Major research advances during those years include development or discovery of:

1. The discovery that viruses are the cause of certain kinds of neurological degenerative diseases, notably the presenile dementias.
2. Computerized axial tomography, and effective non-invasive scanning technique for diagnosis and monitoring of head injuries, stroke, brain tumors and other disorders.
3. Precise identification of specific enzyme defects associated with hereditary metabolic diseases affecting the CNS, such as phenylketonuria, galactosemia, and the group of sphingolipid storage diseases.
4. Neuroradiologic diagnostic techniques including pneumonencephalography via the ventricular or spinal route and use of radiopaque dyes for myelography and angiography to visualize the spinal canal and the cerebral blood vessels, respectively.
5. Electromvography for diagnosis of muscle and peripheral diseases.
6. Radioisotope scanning techniques for diagnosis of brain tumors and other CNS lessions.
7. Control of nervous system infections such as meningitis and bacterial and fungal CNS infections including those associated with neurosyphilis and TB.
8. Sabin and Salk vaccines for eradication of acute polio.
9. Ergotamine treatment for migraine-type headache.
10. Surgical techniques to treat aneurisms of cerebral blood vessels and of occluded cerebral arteries.
11. Copper restriction as dietary control of Wilson's disease.
12. Cure of pernicious anemia with associated subacute combined degeneration of the spinal cord using vitamin B12.

13. Development of diagnostic tests using small samples of blood to detect patients and carriers of the various sphingolipid storage diseases and to permit identification of the fetuses at risk during pregnancy so that genetic counseling can be available to the prospective parents.
14. Use of anticoagulants in treatment of stroke.
15. Differentiation of criteria and of specific treatment for thrombotic stroke, embolic stroke, and hemorrhagic stroke.
16. Development of intensive care procedures for treatment of acute stroke.
17. Development of surgical procedures for treatment of embolic stroke and for treatment of ruptured cerebral aneurism.
18. Development of non-invasive techniques for measuring cerebral blood flow.
19. Development of head injury and spinal cord injury acute care units.
20. Use of hypothermia in the treatment of acute injury to central nervous system.
21. Use of corticosteroids in the treatment of acute injury to central nervous system.
22. Development of intracranial monitoring of cerebrospinal fluid pressure.
23. Use of drugs to lower intracranial pressure.
24. Development of objective methods for testing spinal cord physical integrity following spinal injury.
25. The surgical treatment of otosclerosis, a major cause of hearing loss and deafness in adult life.
26. Improved therapy for aphasia (loss of language) secondary to stroke or head injury.
27. The development of hearing diagnostic tests for the young.
28. The elimination of mastoiditis as a public health problem.
29. The development and improvement of hearing aids and other auditory prosthetic devices.
30. Development of shunt procedures for the treatment of hydrocephalus.
31. Development of electronic monitoring equipment for evaluation of epilepsy.
32. Development of gas chromatographic methods for monitoring antiepileptic drug blood levels.
33. Development of measles vaccine.
34. Development of phenylketonuria test for prevention of one form of mental retardation.
35. Use of L-Dopa and decarboxylase inhibitors for the treatment of Parkinson's Disease.
36. Development of methods to treat and prevent decubitus ulcers in paralyzed patients.

National Institute of Arthritis, Metabolism and Digestive Diseases

INTRAMURAL RESEARCH ACHIEVEMENTS

1970.—Institute scientists detected Australia antigen in the blood of 74 percent of patients with serum hepatitis, where lower incidence was found in the blood of patients with infectious hepatitis. The data suggest that Australia antigen may be hepatitis virus itself, a finding that might lead to development of a vaccine effective against both types of hepatitis. (1970)

Institute scientists also produced a very practical health-saving advance, development of a sensitive test for screening blood donors and blood products to help eliminate the presently ubiquitous risk of transmitting hepatitis by transfusion of blood containing viable hepatitis virus. (1970)

Investigators have shown that insulin exists in two distinct forms in man: "little insulin," which is indistinguishable from the hormone produced by the pancreas, and "big insulin," which is a larger molecule and comprises up to 50 percent of the insulin in the circulation. (1970)

An easy, quick method for diagnosing cystinosis, a serious human hereditary disorder of metabolism, has been devised by Institute scientists, employing tissue taken from the eye for the detection of unusual quantities of cystine, an amino acid found in many proteins. (1970)

1971.—Investigators have produced a form of arthritis in pigs which resembles human rheumatoid arthritis by injecting them with certain mycoplasma organisms. Significant evidence suggesting antibody production in the joints is also shown. (1971)

1972.—Institute researchers have pinpointed the biochemical defect in Hurler's syndrome, an inherited metabolic disorder marked by skeletal deformities ("gargoylism"), mental retardation, and early death. The implications of this finding

are far-reaching and include the possibility that early correction of the flaw might prevent, or at least ameliorate, the disorder's bizarre clinical manifestations. (1972)

1973.—A group of American scientists, including an NIAMDD investigator, has confirmed British scientists' findings of the value of gold salts as a recognized treatment for rheumatoid arthritis. In addition, the American group has demonstrated that long-term gold salt therapy, for 6 to 24 months, also is beneficial, especially when compared with placebo-treated patients whose conditions worsened over the same period of time. (1973)

An NIAMDD scientist has employed affinity chromatography in an as-yet preliminary "artificial liver" device to remove bilirubin and other protein-bound substances from plasma and blood, a technique that may prove useful in patients with liver failure, in cases of intoxication with protein-bound drugs, or in specific metabolic defects. (1973)

Investigators have shown via animal studies that zinc is necessary for normal mobilization of vitamin A from liver, and for maintenance of normal plasma levels of vitamin A, and that zinc supplementation may be of value in vitamin A-resistant deficiency states. (1973)

1974.—An Institute scientist has described significant inflight losses of calcium, nitrogen, and phosphorus in the Skylab astronauts, which suggest that in truly prolonged space flights (such as 18 to 36 months' trips to Mars) human musculoskeletal system function may be seriously impaired unless effective, protective countermeasures can be developed. (1974)

Intramural scientists have shown that in cystic fibrosis there is a severely decreased mucociliary transport (the gradual sweeping upward-and-outward of inhaled particles, bacteria, and mucus) in the lung and trachea, considered a serious contributor to the eventually fatal chronic lung disease of such patients. They have demonstrated that administration of a new drug, Terbutaline, significandy increases tracheal mucous outward velocity and thus may be of therapeutic significance in cystic fibrosis. (1974)

EXTRAMURAL RESEARCH ACHIEVEMENTS

1970.—A 10-year multi-clinic study supported by the NIAMDD has obtained evidence to indicate that several of the widely used oral anti-diabetic drugs may actually shorten the life-span of patients with adult-onset diabetes because of premature cardiovascular death. At the same time they do *not* affect the course of the disease any more than plain dieting. (1970)

An investigator at the University of Texas has reported that diabetes is characterized by excessive secretion of the hormone glucagon, in addition to insulin deficiency, and thus may be a *bi*hormonal disorder. This opens new approaches to the treatment of diabetes. (1970)

1971.—Human growth hormone, the anterior pituitary hormone which controls such life processes as growth and varied aspects of metabolism has been synthesized by an investigator at the University of California, San Francisco. (1971)

A University of Wisconsin scientist has shown that vitamin D is converted in kidney tissue to the ultimate biologically active form of the vitamin—1,25-dihydroxycholecalciferol. The latter is therapeutically effective in "vitamin D resistant" rickets and in the bone disease which accompanies kidney failure. (1971)

A scientist at the Mayo Clinic has shown that long-term oral administration of a primary bile acid—chenodeoxycholic acid—results in dissolution of long-standing cholesterol gallstones. (1971)

1973.—At the State University of New York Buffalo, an investigator has devised a simple, practical and inexpensive method for detecting sickle-cell disease and other hemoglobin abnormalities, which utilizes dried blood specimens on filter paper (a method employed in mass screening of newborn infants for phenylketonuria, or PKU), (1973).

1974.—At the University of California, Los Angeles, a scientist has demonstrated an increased prevalence of the histocompatibility antigen—W27—in patients with juvenile rheumatoid arthritis, suggesting an inherited etiologic link with two other forms of arthritis—Reiter's disease and ankylosing spondylitis, (1974).

Scientists at several institutions have demonstrated simultaneously that metiamide, an antihistamine drug developed in England, effectively blocks gastric acid secretion and thus might be of value in peptic ulcer therapy, (1974).

1975.—At Massachusetts General Hospital investigators have reported complete clearing of skin lesions in 21 patients with severe psoriasis, following oral administration of methoxsalen and exposure to a newly developed, high-intensity, long-wave ultraviolet light source, (1975).

National Institute of General Medical Sciences Research Accomplishments for the Past Five Years

1. As a result of the Boston Collaborative Drug Surveillance Program, supported by an NIGMS contract since July 1966, several important epidemiological associations and adverse drug reactions have been discovered. An extensive data bank on the vital statistics of hospitalized patients in the Boston area has been accumulated in a central computer facility, including complete records of all medications received together with estimates of the efficacy and/or toxicity of those drugs in each patient. Discovery of a strong negative association between regular doses of aspirin and nonfatal myocardial infarction, based on 776 hospitalized heart attack patients and 14,000 patients with other diagnoses. This research has led to large-scale prospective studies by the NHLI of aspirin's potential value in prevention of myocardial infarction (Jick) 1974.

2. Schistosomiasis is a dangerous disease of great importance in many areas of the world, particularly developing countries. Many of the compounds which have antischistosomal activity also have been shown to be carcinogenic and/or mutagenic.

Dr. Ernest Bueding and his co-workers at Johns Hopkins University have obtained evidence that within a class of schistosomicidal agents, the thioxanthenes, suitable chemical modifications can maintain or even enhance chemotherapeutic activities, while markedly reducing the acute and long-term (carcinogenic and mutagenic) toxic effects; for example, the acute toxicity of one of these compounds (8-chloro-5-hydroxymethyl benzothiopyranoindazole) is 14 times lower than that of hycanthone, a widely used antichistosomal drug in man. In addition, this compound has only 1.5% of the mutagenic activity of hycanthone and, in contrast to the latter, produces parasitological cures when administered as a single oral dose to mice and hamsters infected with *Schistosoma mansoni.* In addition, the compound proved to have prophylactic activities, i.e., its administration prevented the development of the infection when mice were exposed to the larval stages (cercariae) of schistosomes. Trials of this promising compound in primates are planned (Talalay, Bending, GM 16492) 1974.

3. While there has been much research on nucleoside analogs which can be used as antineoplastic agents, it has also been found that, because of their specific ability to inhibit nucleic acid biosynthesis they are potentially useful in disorders other than cancer whose pathogenesis involves accelerated nucleic acid biosynthesis and cellular proliferation. One of these agents, 2′,3′,5′ triacetyl 6-azauridine (azaribine) has been found to be extremely effective in the treatment of severe recalcitrant psoriasis and psoriatic arthritis. Psoriasis is generally a mild skin disorder, but it can be severe and debilitating, with involvement of the skeletal and cardiovascular systems. Although several inhibitors of nucleic acid biosynthesis are effective in producing remissions in severe psoriasis, most are very toxic and can result in serious damage to vital organs such as the liver, gastrointestinal tract, and the hematopoietic system. Azaribine has been found by several NIGMS grantees to be as effective as some of the other agents and yet to have only minimal toxicity. Their extensive clinical studies provided the information necessary to prove efficacy and safety of azaribine. This new drug is scheduled for commercial distribution in the near future (McDonald, Pearson, GM 15759) 1973.

4. Patients remote from medical centers often have their X-ray films read only after long delays. To overcome this problem, the prototype of a new transmission, reproduction and storage technique has been developed at MIT that provides high quality facsimiles of radiological films that are virtually indistinguishable from the originals. These films can be sent over telephone lines to a central hospital facility where the signals are then reconverted into an accurate copy of the original film in a matter of minutes for reading by a radiologist (Eden, Massachusetts Institute of Technology, GM 19428-02) 1975.

5. Since 1974, several NIGMS investigators have successfully treated severe burns involving 80% Total Body Surface with 70% third degree burns. Previously the mortality rate was 100%. Their technique include skin transplantation, immunosuppression, rapid fluid replacement, hyperalimentation, and a bacteria-controlled environment. Fluid balance is achieved within 24–48 hours. The survival of skin grafts, permitting growth of healthy skin to cover the burned areas,

has been enhanced by the administration of immunosuppressive agents. Bacteria-controlled nursing environment is used with carefully regulated temperature and relative humidity. Hyperalimentation restores the necessary amounts of protein. The recovery rate by these methods has been 64% (Baxter, GM 21268I; Burke, GM 21700) 1973.

6. Silver sulfadiazine (Ag SD) is a new (1973) highly successful topical antimicrobial agent for the treatment of burns. It has been tried on over 10,000 patients throughout the world with less than ten exhibiting adverse reactions. Ag SD activity is not diminished by wound contaminants or metabolites and its broad action inhibits the growth of many bacteria and fungi. Unlike other agents, Ag SD is non-painful and does not stain. It forms a reservoir in burned tissue delivering bacteriocidal levels of silver over long periods of time. Less than 10% of the sulfadiazine is released and absorbed. No renal or hematologic toxicity has been reported. In conjunction with parenteral treatment, it has been very effective. For example, in Dallas, there have been only seven deaths from infection in 315 patients with burns up to 60% TBS (Fox, GM 18275 and Baxter, GM 21681) 1973.

7. The development of highly reliable assays for prenatal diagnosis of Tay-Sachs Disease and for determining the carrier status of individuals within a population at risk for the disease. This work has led to the development of community screening programs, and the possibility for prevention of a condition which is uniformly fatal in infancy (Seegmiller, O'Brien, and Okada, GM 17702) 1970.

8. Discovery of the underlying defect in familial hypercholesterolemia, with important prospects for specific diagnosis and therapy. Persons affected by this disorder manifest a two-to-threefold elevation of plasma cholesterol from birth and the great majority die prematurely from coronary disease. It currently is estimated that the condition occurs in one in 500 of the United States general population (Goldstein, GM 19258) 1973.

9. Discovery of a hereditary enzyme defect which in affected persons results in a strong predisposition to lung cancer. Possibly as much as one-third of the United States population is so affected. A simple blood test is being developed and hopefully will enable physicians to diagnose the condition. Affected persons, forewarned, thus could exercise special precautions with regard to smoking and exposure to other carcinogens (C. Shaw, GM 15597) 1972–1973.

10. Discovery and elucidation of the chemical nature, structure, and formation of long rod-like tubules, called "microtubules" which occur within all cells and have an important role in cell division, in the motility of sperm, in the beating action of cilia within the respiratory passages, and in the maintenance of cell form and structure (E. Taylor, GM 10992; J. Rosenbaum, GM 14642; I. Gibbons, GM 15090; L. Tilney, GM 18100) since 1970.

National Institute of Child Health and Human Development

Research Accomplishments Within the Past 5 Years

EXTRAMURAL PROGRAMS

Population

1. The Institute completed a clinical trial of chemical contraceptives for men. (Clinical trial was completed in 1974 as part of an on-going research activity.)

Monthly injections of a synthetic male hormone combined with daily oral administration of a synthetic male hormone have resulted in significant decreases in sperm numbers in a majority of the men. Such low sperm numbers are believed to be incompatible with fertility. This advance paves the way for an intensified search for new male antifertility chemicals and eventually a safe and effective male contraceptive.

2. Testing of a soft fluid-filled IUD is being accomplished. (Preliminary results were reported in 1975; research is continuing.)

Preliminary results have been encouraging in terms of both safety and efficacy. A comparison of this IUD to presently marketed IUD's will soon be possible. This IUD is potentially safer and more effective than many other forms of contraception and could provide a very desirable family planning method.

3. Effects of presently used oral contraceptives on several parameters known to be risk factors in disease have been identified. (This is a continuing research effort.)

Hypertension, stroke, decrease in glucose tolerance, and many other medical effects have been associated with oral contraceptive use by women. This research

effort has led to the development of safer oral contraceptives, the users' knowledge of risks and alternative family planning measures, and the physicians' knowledge of risks and the necessity to evaluate and monitor patients carefully. This research has also shown the need for additional surveillance and given indications for safer drug applications in the future.

4. Medical effects associated with vasectomy have been identified. (Research advances are continuing in this area.)

The presence and increase in two kinds of antibodies, for example, have been identified in men who have experienced vasectomy. This research proves that there are consequences of vasectomy other than fertility control. Therefore, there is a need to investigate further the consequences of vasectomy to determine if this family planning method is associated with any adverse medical effects.

5. Development of an intravas device to easily achieve reversible vasectomy has progressed to animal models. (This is a continuing endeavor.)

Significant new knowledge of the basic physiology of the male reproductive tract is providing new ideas on possible ways of limiting male fertility without interfering with the other functions of the testis or with libido. Development and testing of devices intended for the achievement of easily reversible vasectomy have resulted in major advances. Some devices have been in place in laboratory animals for more than one year and have been found to be effective. Preliminary data indicate that fertility is present when the device is in the open position and is not present when it is in the closed position. Thus, this device is potentially viable as a new method of contraception and as an alternative to the presently available types of vasectomy, which are generally not reversible.

Perinatal Biolgoy and Infant Mortality

1. Maternal diseases and complications that can increase infant morbidity and mortality have been identified. (These results are from a continuing research effort.)

In part through Institute research, it is well known that infant morbidity and mortality can be increased by maternal disease and complications of pregnancy such as poor nutritional status, diabetes, high blood pressure, anemia, drug addiction, smoking, and the psychic stress of pregnancy. Prenatal care practices have improved significantly in recent years as a direct result of this research. Infant morbidity and mortality rates have been declining, in part due to prenatal care although cause and effect data are difficult to obtain. Research in this area will continue to probe mechanisms to prevent these complications because scientific opportunities and expectations are encouraging for the health of both the mother and child.

2. Possible causes of the sudden infant death syndrome (SIDS) have been identified. (These accomplishments have evolved since 1970.)

Until this decade, SIDS, or crib death, was a complete mystery. In the past few years, new leads have evolved that indicate that SIDS might be related to: apnea, infection, and heart rate changes; developmental maturational lag; oxygen deficiency; lack of sleep; abnormality in the brain stem; immaturity of the nervous mechanism controlling heart function; and inadequate lung responses. Until 1974, it was believed that SIDS victims had been basically healthy babies. From data obtained and evaluated in 1974 and 1975, it now appears that SIDS victims had not been completely healthy. Autopsies indicate that many victims had a previous history of oxygen deficiency. All of these leads may eventually provide clinical opportunities to save up to 10,000 infants per year.

3. It has been hypothesized that babies with abnormal sleep patterns may be at risk for the sudden infant death syndrome (SIDS). (This fact was reported in 1975 as part of a major research effort which has evolved during this decade.)

The occurrence of abnormal sleep patterns in SIDS continues to yield important information pertinent to learning more about the cause and underlying mechanisms of this syndrome. It has been determined that an abnormal sleep pattern (sleep-apnea) is affected by the variances known to influence the incidence of SIDS—low birth weight, shortened gestation, and mild upper respiratory infections. This is clinically significant because infants with a sleep-apnea can be identified and their subsequent risk for SIDS assessed. Hopefully, through close medical management and enhanced surveillance, death of infants with sleep related apnea may be prevented.

4. It has been found that too much exercise during pregnancy can reduce oxygen supply to the fetus. (This was reported in 1975 as a continuing part of a major research endeavor.)

The finding is important because the daily activities of pregnant women impose considerable demands on maternal oxygen consumption and cardiac output. The importance of understanding the physiologic effects of exercise are being emphasized in order to provide maximum safety for fetal growth and development.

5. Prenatal and postnatal diagnostic and treatment advancements have been made. (These results are parts of continuing projects.)

As a direct result of research in the NICHD's Perinatal Bilogy and Infant Mortality and Mental Retardation programs many diagnostic and treatment techniques have been put into clinical use. Two examples are outstanding. Because of a diagnostic procedure called amniocentesis, which was recently developed and more recently put into widespread clinical use, it is now possible to detect *in utero* many conditions such as mongolism and Tay-Sachs disease. Secondly, within the past three years significant new knowledge has emerged regarding low birth weight infants, a group with concentrated morbidity and mortality. Both premature infants and those of low birth weight for gestational age have benefited from studies on detection of fetal maturity *in utero*, induction of pulmonary maturation, recognition of fetal and neonatal growth retardation, and congenital and acquired infectious processes. On-going studies of genetic factors in low birth weight infants are providing a wealth of information. Clinical advances in the recognition and treatment of jaundice, respiratory distress syndrome, thermal regulation, chemical adaptation and infection in the newborn have resulted from these recent investigations. These findings are helping to save many infant lives.

Growth and Development

1. Identification has been made of relationships of nutrition to human development. (Research in this area is a continuing process.)

Research has resulted in new knowledge regarding the adverse impact of malnutrition in pregnancy in terms of the development of the progeny, and data are now becoming available concerning the beneficial effects on child development of nutritional supplementation during pregnancy. As the Institute makes these data available, the worldwide impact of healthier pregnancies and offspring will become readily apparent. Recent research has also provided an improved description of physical growth and body composition in relation to the age, sex, and nutrient intakes of normal infants receiving either breast milk or cow's milk; this will enable health care personnel to make more informed decisions concerning the nutrition of infants.

2. A discovery has been made that infants apparently perceive vocalized sound somewhat in the way adults do. (Reported first in 1971—Follow-up and expanded studies are continuing.)

Recent studies have shown that within the first week after birth infants are able to discriminate between speech sounds such as "bah" and "gah". This is important in itself, but the learning implications are astounding because these infants perceive the sounds in an all-or-none categorical manner, as do adults, hence, presumably, in a linguistic mode as opposed to a purely acoustic one. Now, children, at a very young age, may be tested and at times treated for hearing, learning, and communicative disorders.

3. A chimpanzee, with the help of a computer, has been trained to talk to people. (This was reported in 1975 as part of a continuing project.)

A three year old chimpanzee named Lana has demonstrated remarkable language learning feats, which have earned her national attention. It is believed that with the aid of a computerized, artificial language called Yerkish (after the Yerkes Primate Center) Lana not only can learn a language, and use it to name objects and convey her needs, but she may also become a major communication resource in the behavioral study of other chimps. Inroads in many fields such as language acquisition and basic animal behavior research may be achieved.

4. Findings regarding the treatment of dwarfism may soon achieve clinical utilization. (Although this is a continuing effort, specific accomplishments have been obtained since 1974.)

In the treatment of dwarfism, physicians must use a natural hormone obtained from human cadavers to help a dwarfed child grow, for example, beyond 4 feet to a height of 5 feet. This natural hormone is highly expensive to produce and is available only in very limited quantities. Now, however, a researcher has been able to analyze the components of this natural hormone. This work takes science considerably closer to the day, perhaps within two years, when laboratories will be able to synthesize a drug as a plentiful and less costly substitute for the growth hormone normally produced in the human body.

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5. It has been found that different parts of the brain are responsible for different kinds of learning. (This is a continuing activity.)

It has been know for a long time some children who learn well in some areas have problems in others. For example, a child may have difficulty with speech or reading but perform well otherwise. Research has been convincing to show that different parts of the brain are responsible for different kinds of learning, and with this knowledge it is hoped that within a couple of years physicians and related personnel will be able to prescribe new clinical methods for helping these children who are having trouble.

Mental Retardation

1. It is known that the incidence of mongolism rises with increasing maternal age; and the NICHD has undertaken an information dissemination campaign. (Educational campaign began in 1974—mongolism research is continuing.)

Investigations have shown that the incidence of mongolism rises with increasing maternal age. The chances of giving birth to a child with mongolism is about 5 times higher for women over 35. It is over 35 times more frequent for women 45 or older. The NICHD initiated and is continuing a national health education campaign aimed at reducing the incidence of mongolism.

2. Development and utilization of a Responsive Teaching Model has been achieved. (This was developed in 1973; utilization is continuing.)

From research with the mildly retarded, scientists have developed a Responsive Teaching Model which is now being applied in schools in nearly every state in the nation. The model, which is a scientific behavior management system, has been extended to the home and other settings with significant impact on social and academic behaviors of normal and handicapped children. The utilization of the techniques by parents should permit more developmentally disabled children to remain in their own homes and communities.

3. An association between maternal alcoholism and abnormal fetal development has been described. (This was reported in 1975 as part of continuing mental retardation and perinatal biology and infant mortality research.)

A pattern of malformation has been observed in children of alcoholic mothers which suggests a strong association between maternal alcoholism and aberrant morphogenesis in the offspring. The affected children manifested developmental delay, microcephaly, prenatal and postnatal growth deficiency and a similar pattern of craniofacial, limb, and cardiovascular defects. Their motor and social performance was more in accord with their mental age, which was moderately to mildly subnormal, than to their chronological age.

4. An automated system for chromosome analysis has been developed. (This was accomplished in 1975 after several years of study.)

The need to develop an automated system for chromosome analysis has been known for several years. The recently developed automated system can be used for research, clinical, and epidemiological studies. It will be particularly applicable in surveys of numerical and structural chromosome changes in newborn infants, and institutionalized populations, following exposure to radiation, chemicals, drugs, and viruses which may cause chromosome breakage.

5. The NICHD has reported findings that institutionalized care of the mentally retarded is not improved significantly by administrative changes. (This is a continuing research program.)

Organizational and other elements affecting the quality of care in institutions are being studied. Unitization—the establishment of quasi-autonomous living units in large formerly centralized institutions—is one of the elements under study. Findings in one facility indicate only minor shifts toward resident orientation through such administrative change and that practices are still largely characterized by rigidity in routines, depersonalization and social distance between residents and staff. It has also been noted that IQ level of residents is strongly associated with the quality of care provided despite the higher staff ratios afforded the more severely disabled. This suggests the need to identify the personality traits of caretaker personnel conducive to resident-oriented care practice.

INTRAMURAL PROGRAMS

Population

1. Advances in methods for detecting and measuring hormones and for measuring biologic effects of these substances have been made. (Research in this area is a continuing process.)

In 1975, three significant advances were made in the area of hormonal control in relation to population and reproduction science. (1) NICHD scientists developed

an inexpensive test for diagnosing pregnancy in the rhesus monkey, a major laboratory research animal that has recently come into short supply in the U.S. Reagents for performing the test are currently being distributed to scientists who use this primate for research in reproductive biology. (2) Researchers have developed the only *completely specific* method for detecting human chorionic gonadotropin, a hormonal indicator of pregnancy, in specimens of human urine. Its clinical applications will be important because a physician will be able to diagnose pregnancy as early as the 8th day after conception; thus pregnancy is detectable unambiguously 3–4 weeks earlier than by using currently acceptable procedures. One of the benefits of early diagnosis of pregnancy will be to assist physicians in diagnosing an ectopic (tubal) pregnancy in a woman with abdominal pain. (3) Scientists have also developed a test tube method for measuring the binding of hormones to their receptors in target cells, and measuring the biological activities of hormones that stimulate ovary and testis. These methods make it possible to study such diverse problems as hormone target cell interactions during growth and development, the structural features required for interactions of hormones in target cells, and the effects of drugs on these interactions. The importance of these assays for practical application in the development of new methods for fertility control cannot be overemphasized.

2. It was found that the pituitary gland is important in prenatal gonadal development. (This was first reported in 1974.)

NICHD scientists developed a surgical method for removing the pituitary gland from the fetal rhesus monkey without interrupting pregnancy. This ablative procedure inhibits the normal fetal maturation of the ovary and testes, indicating that the fetal pituitary is important in prenatal gonadal development. This finding is significant because it further paves the way for diagnosing and treating some of the problems of infertility, abnormal sexual development, and fetal development.

3. Development of clinical tests to study infertility have been progressing. (Research is of a continuing nature in this area.)

A series of clinical tests has been developed which appears to reflect accurately disordered function of the hypothalamus, a small area at the base of the brain which regulates metabolic functions including pituitary secretion. These tests have been utilized to study patients with Anorexia Nervosa, a disorder associated with profound weight loss and cessation of menstrual periods in young women. Institute findings suggest the disorder results from hypothalamic dysfunction rather than from psychological problems as previously thought. Thus, these patients provide a new human model for the study of hypothalamic control of pituitary function. This research may eventually result in identifying the proper treatment of those suffering from Anorexia Nervosa.

4. Identification and treatment of some types of infertility have been achieved. (Research in this area is a continuing process.)

The Infertility Clinic, established in 1971, provides an environment for evaluating problems of infertility. One of the first scientific results from this clinical research was a description for the first time of the pathogenesis of the short luteal phase as a cause of female infertility, and its successful treatment.

Maternal and Child Health

1. A statistical procedure to relate risk factors to disease was developed. (This was reported in 1975.)

A new statistical procedure has been developed to relate several risk factors to the disease with which they are linked so that physicians can predict a patient's risk of disease from knowledge of the characteristics of the individual. Applications have been made to the etiology of stroke in women.

2. Identification of the regulation of blood sugar levels has been accomplished. (This was reported in 1975.)

Studies in an animal model system have shown differences in the regulation of blood sugar levels in neonatal and adult animals. In the neonate, it was noted that milk sugar plays a role in this process, and this simple substance will be used in attempts to treat hypoglycemia, a serious disease state related to and in many cases leading to diabetes, of the newborn infant.

3. NICHD scientists have developed a vaccine which has the potential to prevent *Hemophilus influenzae* meningitis. (This research is of a continuing nature.)

The leading cause of acquired mental retardation, *Hemophilus influenzae* meningitis, may be fully preventable if findings of the Institute's scientists are borne out in recently initiated human trials. NICHD research with the organism has resulted in the development of a vaccine, and in 1974 a clinical trial of this vaccine began under the Institute's auspices.

4. Mother-child stimulation interactions were defined in relation to child development. (This was reported in 1974.)

Because of the ever increasing number of working mothers whose children have substitute caretakers for part of the day, one research accomplishment has important social and family implications. The mothers and caretakers were compared on scientific measures of infant stimulation and interaction important to infant development. Mothers provided more stimulation than surrogates on all measures tested. Nonetheless, the difference did not have a measurable effect on functioning when the children were tested at 18 months.

5. Methods were developed to test substances which are potentially dangerous to the fetus. (This is a continuous research endeavor.)

Investigators in the intramural program have been systematically studying drugs and environmental contaminants which can cross the placenta to influence the fetus, and the mechanisms by which these agents act. It was recently discovered that fetal cells in tissue culture respond, in terms of capability of enzyme induction, in the same way as the intact animal, and reflect genetic variations in this trait. Thus, by means of studies in cell culture, the toxic effect in the intact animal of the substance being tested could be predicted. This finding may make it possible to assess the potential teratogenicity (the tendency to produce malformations) of various drugs or other foreign compounds in genetically different individuals.

6. A discovery of an effect of cigarette smoking by pregnant women was made. (This was reported in 1973.)

Scientists found that cigarette smoking by pregnant women induces enzyme activity in the placenta. Although a direct cause/effect relationship has not been proved scientifically, this enzyme activity may be related to the reduced weight of infants born to cigarette smoking mothers. This study in conjunction with other factors such as concerns about the high mortality and morbidity rates among low birth weight babies and the general effects of environmental contaminants on the fetus, has produced two results: physicians and others are strongly advising pregnant women not to smoke; and scientific interest in environmental contaminants has been further stimulated.

National Institute of Environmental Health Sciences

RESEARCH ADVANCES, 1970–75

During the last five years, NIEHS has been involved in research on a variety of environmental health problems, many having major significance for man's health.

Dioxin

One example concerns the contaminant "dioxin" (2,3,7,8-tetrachloro-dibenzo-p-dioxin or TCDD) found in commercial samples of the once commonly used herbicide 2,4,5-T (2,4,5–trichlorophenoxyacetic acid). At first scientists believed 2,4,5–T itself affected the development and viability of mouse and rat fetuses. Following work done by an NIEHS team, however, a contaminant in the 2,4,5-T was discovered to be the real culprit. This contaminant was dioxin or TCDD. TCDD has since been revealed as one of the most toxic substances known to man. After the NIEHS research was reported, the Environmental Protection Agency restricted use of 2,4,5-T.

Subsequent studies by NIEHS researchers revealed an increased susceptibility in mice to bacterial infection as a result of exposure to TCDD. These studies showed that extremely low levels of TCDD, which do not produce clinical or pathological change, still have the capacity to affect host defense. These findings are significant in that humans may be exposed to environmental contaminants such as TCDD in minute quantities and, therefore, may be rendered more susceptible to certain types of infectious agents.

Bis (Chloromethyl) Ether

Work done by a team of scientists supported by an NIEHS center grant at New University Institute of Environmental Medicine revealed a significant hazard to human health which could then be controlled or removed from the environment. This hazard was associated with bis (chloromethyl) ether, a colorless chemical that is one of a family of organic chemicals commonly called halo ethers. These compounds are used in large quantities in the chemical industry for polymerization and stabilization of polymers.

These investigators suspected on the basis of the chemical structure of the bis (chloromethyl) ether that this compound might be carcinogenic, capable of causing cancer. Testing the compound in mice and rats supported this theory. Bis (chloromethyl) ether is a potent carcinogen when applied to the skin of mice or when injected in mice or rats. In fact we now know that very small concentrations in the air may cause a significant increase in certain kinds of lung cancer. Thus, we cannot be reassured by the knowledge that most of these compounds are present in the environment at very low concentrations. And the fact that later testing showed mice may develop lung tumors after inhalation of very low concentrations of the compound is particularly important because workers in the chemical industry probably have been exposed to fumes of the compound.

At this time, it is impossible to determine how many people have been exposed to either bis (chloromethyl) ether or its related compounds. At least 3000 men are known to have been exposed in the chemical industry. Federal agencies and the industries involved are keeping these men under close surveillance as a group with above average expectancy of developing cancer.

Studies by the NYU team on the health of workers in six chemical plants have shown that workers run a two-and-one-half to three times greater risk of lung cancer than a control group of people not exposed to bis (chloromethyl) ether. Since these studies, scientists have found an excessive number of cases among chemical workers in Germany and Japan. In one group, all the lung cancer deaths occurred in workers subjected to heavy exposure to the chemical for five or more years.

Because almost the entire production of bis (chloromethyl) ether is used by the corporation that makes it and because very little is sold outside the plant, bis (chloromethyl) ether until recently appeared to be mainly an occupational health problem and not a general environmental health problem for the entire population. Not long ago, however, several halo ethers appeared in the Ohio River water, Rhine River water, and a variety of other rivers that flow through major industrial areas. These compounds were found to be present in discharges from chemical plants in the vicinity and subsequently were detected in municipal drinking water. Effective steps are being taken by regulatory agencies to limit such exposure, as well as exposure in the work place.

Asbestos

Another problem that concerns NIEHS is how to protect the population from hazards associated with compounds we already are using that seem essential to our everyday living and continued economic development. This dilemma is sharply apparent in the case of asbestos. It is now clear that failure to carry out research on this problem in the 1930's and 1940's left us with a terrible legacy of perhaps tens of thousands of asbestos-related deaths.

Approximately nine years ago, the NIEHS began to support rather extensive research on asbestos. As a result, we now know the consequences of uncontrolled industrial use of the material. We still are faced, however, with the critical task of finding ways of inactivating the dust already fixed in our bodies. It is urgent for us to find substances which can alter the dusts already deposited in human lungs and prevent otherwise inevitable disease. There is reason to hope that Federally supported research can succeed in this quest.

Since 1973, the National Institute of Environmental Health Sciences has been supporting an Environmental Health Sciences Center which concentrates on asbestos research. This Center is located at Mount Sinai School of Medicine, New York, and is under the direction of Dr. Irving J. Selikoff, a pioneer in asbestos epidemiology. It was to Dr. Selikoff, incidentally, that the Environmental Protection Agency turned recently for recommendations when confronted with asbestos contamination of drinking water in Duluth, Minnesota.

Recently Center personnel reported that analysis of representative samples of spackling, patching, and taping compounds has shown that some contain asbestos minerals as well as other potentially harmful substances. Measurements suggest that home repair or construction work involving use of such materials may result in exposure to dust at concentration sufficient to produce disease.

Fifteen representative samples of consumer spackling and patching compounds and ten of industrial drywall taping compounds were analyzed for asbestos mineral content. Four of the spackling and patching compounds were purchased at hardware stores in the New York City area in 1972 or earlier, and the remainder in January 1974.

Spackling and drywall taping compounds consist of finely-grained white powder or premixed pastes. Although Plaster of Paris is supposedly the major constituent,

other light-colored materials including clays, micas, quartz, talc, and ground limestone supplement or replace the plaster in many formulations. Additionally, chrysotile asbestos is added to some products, apparently because these minute fibers act as reinforcing agents.

Analysis of the 15 consumer spackling and patching samples has shown that 5 contained appreciable amounts of chrysotile or other asbestos minerals, as did 9 of the 10 industrial products. Many contained substantial amounts of quartz, talc, and other minerals. Once embedded in the lungs, quartz or silica particles—like those of asbestos—may never be removed. They can produce chronic orbstructive and fibrotic diseases after prolonged exposure. Talc also can produce pulmonary fibrosis.

Air samples obtained during the use of asbestos-containing spackle compounds were analyzed and showed concentrations frequently in excess of the current occupational standard for permissible asbestos exposure levels. Fiber counts measured during mixing for example were found to be 7–12 times greater than the standard. Detectable fiber concentrations were found in adjacent rooms during mixing, and fibers were still suspended in the room air at least 15 minutes after mixing had ceased.

These findings suggest the possibility of significant asbestos exposure during home construction repair. Additional work by the Center personnel suggests that members of the entire household or other occupants of a building may also inhale asbestos fibers. This could occur during mixing, sanding, or cleaning up of debris.

These results are alarming when considered in relation to other evidence being accumulated by the Mount Sinai group that indicates that far less than the intense exposure of the work environment is capable of producing asbestos-related disease. X-ray examination of 210 family contacts who lived with the men who produced asbestos insulation at a Paterson, New Jersey, plant from 1941 to 1954 has shown that 40 percent have the kinds of abnormalities in their lungs common to asbestos workers. In some cases, the worker had been at the Paterson plant for only a few days.

Thus, it appears likely that the use of spackling, patching, and taping compounds containing appreciable levels of asbestos minerals in home repair work may expose the user, and other members of the household, to concentrations of asbestos that may lead to disease.

Ozone

Some scientists are warning that a group of aerosol propellants called chlorofluorocarbons may be damaging the earth's protective layer of ozone. Chlorofluorocarbons, used under pressure to eject sprays, are found in many household products including some hair sprays, deodorants, antiperspirants, and pharmaceuticals. They are also used as refrigerants.

Some experts have suggested that chlorofluorocarbons break down under the influence of sunlight in the earth's upper atmosphere, releasing free chlorine that then acts to reduce the abundance of ozone. Many believe the depletion of ozone, which absorbs the most lethal wavelengths of ultraviolet radiation, could lead to a worldwide increase in skin cancer incidence.

Since the aerosol sprays came into extensive use, a sharp increase in the amount of chlorofluorocarbons in the upper atmosphere has been observed. This finding has triggered concern about the possibility of serious environmental health hazards resulting. A ban on the use of chlorofluorocarbons in aerosols is currently under study. NIEHS has supported much of the research that has made it possible to begin assessing the effects of changes in the ozone shield on man's health. Currently NIEHS scientists are working with the Council on Environmental Quality and the National Science Foundation, advisory groups to the President, to determine the extent and environmental effects of possible changes in the earth's protective ozone shield.

Ozone and Nitrogen Dioxide

Another example of NIEHS work on ozone concerns studies underway virtually since the opening of the Institute in 1966. These studies have now uncovered strong evidence that ozone and another pollutant in our environment—nitrogen dioxide—are contributing, if not primary, causes of pulmonary emphysema and chronic nonspecific pulmonary disease. In addition to protecting us from the most harmful of the sun's rays, ozone can adversely affect our health.

A part of the picture establishing the sequence of events of ozone and nitrogen dioxide toxicity was provided by NIEHS grantees who produced an experimental

facsimile of human emphysema in rats. They also showed that ozone is approximately twenty times more toxic than nitrogen dioxide. In fact within a few hours of exposure to less than 0.5 part per million ozone—a concentration readily achieved at peak traffic hours in some urban areas—considerable reaction in the lung becomes apparent.

Other grantees found that the focal points of damage at all levels of exposure to ozone in the rat are the small airways of the lung. Still others discovered that the carbonyl compounds that begin to circulate in the blood stream shortly after ozone exposure may serve as a basis for early detection of ozone damage by simple chemical techniques.

While all these studies establish rather clearly what happens in ozone and nitrogen dioxide induced disease, the research of other NIEHS grantees encourages the belief that much of the damage induced by these two pollutants at low levels can be prevented and perhaps reversed in the early stages. Some grantees have demonstrated that lipid antioxidants, particularly vitamins A and E, protect against ozone toxicity; others that certain minerals, particularly zinc, may useful for this purpose. These findings are particularly important as emphysema has led to death for an increasing number of people since 1950, and chronic nonspecific pulmonary disease is now a leading cause of disability among adult males.

To complete the picture of ozone and nitrogen dioxide toxicity, clinical evaluations must be made of vitamins A and E, zinc, and other compounds, as well as combinations of these in test animals and eventually human populations at risk of toxic exposures. Through these efforts, we may be able to conquer the diseases the two pollutants cause.

DES

NIEHS studies with DES (diethylstilbestrol), a synthetic hormone, have emphasized the unique sensitivity of the embryonic period to chemical insults that may result in infertility and perhaps cancer later in life.

Although many compounds are continuously introduced into our environment, few of them have been examined for their potentially toxic effects on reproduction and development. Virtually nothing is known about the effects of exposures to common drugs and chemicals occurring before birth on the development of the offspring after birth.

NIEHS scientists have been using mice to study the effects of environmental agents on reproductive tract function. In their work with DES, a common environmental chemical currently used as a livestock food additive and "morning-after" contraceptive, they demonstrated that prenatal or before birth exposure to DES adversely affects the reproductive capacity of the female offspring. This effect is dose-related and is due in part to the relative inability of the female offspring to ovulate. During the prenatal period oocytes (reproductive cells) undergo division in man and in laboratory rodents, and at that time they are especially susceptible to chemical intervention.

These researchers also found that the male offspring are sterile following prenatal exposure to certain doses of DES. Test results suggest that DES affects the same embryonic tissues in both male and female fetuses and results in postnatal defects in both sexes. The reproductive tracts in the prenatally drug-exposed offspring have lesions which include changes in cell types and/or tumors.

In light of these results in rodents, the incidence of genital tract abnormalities in young men whose mothers were treated with DES during pregnancy may be of clinical importance. In fact, researchers at the Chicago Lying-In Hospital recently reported reproductive tract abnormalities among sons born to women who had received DES.

The results of the NIEHS studies may be pertinent to the development of an animal model to study the reproductive tract lesions reported in young women whose mothers had been given DES during pregnancy to prevent abortion. Such a model could permit more rapid testing of the compounds's teratogenic activity and could hopefully lead to the development of a way to predict for these toxic effects.

Mutagenic agents

Discovery of cancer among workers exposed to vinyl chloride (a gas from which polyvinyl chloride is made) emphasizes the need for better ways to evaluate other potential hazards in the environment prior to man's exposure. These hazards include mutagenic agents or agents that cause genetic damage. This damage may take many forms. It may result for example in chromosome alterations that can

cause spontaneous abortions or an increase in inheritable diseases such as hemophilia.

Development of short-term qualitative tests evaluate the thousands of man-made chemicals already in the environment that have never before been tested for mutagenic activity is the focus of effort by a group of NIEHS scientists. These NIEHS researchers have been working on *in vitro* or test tube techniques for metabolic activation which would allow mammalian metabolites (often the active mutagens) to be tested, as well as the original compound. Through use of such techniques the necessity for using whole animals for screening could be avoided and reserved for obtaining quantitative data required for risk confirmation and evaluation.

Short-term tests for determining mutagenic activity are widely regarded as a sensitive initial method of quickly and cheaply screening chemicals and consumer products for possible toxic effects and of singling out suspect compounds for more detailed evaluation in higher organisms. Because exploratory testing of environmental chemicals and other compounds is turning up new examples of genetic activity in products in widespread use this capability is needed. For example almost all commercially-available hair dyes were recently discovered to be genetically active in some of the newly-developed short-term tests. The potential hazard for the estimated 20 million people in this country alone who dye their hair is not yet known. NIEHS has already initiated studies to determine whether hair dyes cause genetic damage in other experimental organisms in order to better evaluate the risk for man.

The short-term tests may offer answers in another area of concern. While the relationship between mutagenicity and carcinogenicity (cancer-causing ability) is still a matter of considerable scientific controversy, contract work—supported by the National Cancer Institute and developed with NIEHS assistance—is clearly showing a high correlation between the two types of activity. Thus the newly-developed short-term tests with microbes in combination with *in vitro* metabolic activation techniques appear to offer a means of detecting potential mutagenic and carcinogenic effects in man.

These tests also offer a potential solution to a problem faced by our major industries. Namely, providing a testing capability for detection of adverse toxicological effects that can be used in early phases of product development. Too often various industries have invested considerable time and resources only to find that a valuable product is carcinogenic in the traditional two-year assay on laboratory animals. Utilization of short-term tests for mutagenicity offers a rapid, inexpensive mechanism for weeding out products with potential adverse effects early in the development process.

The compound AF–2, the nitrofuran derivative widely used as a food preservative in Japan beginning in 1965, exemplifies the capability of this approach. AF–2 was first determined to be mutagenic in the newly-developed short-term tests over a year ago. Much later it was found to be carcinogenic in mice. As a result AF–2 now has been eliminated from food preservatives in Japan. Vinyl chloride also has been found to be genetically-active in these tests. Had this activity been determined years ago the vinyl chloride hazard to industrial workers and the population in general might have been avoided.

Vinyl chloride's genetic activity in these tests reemphasizes the need to develop better methods for determining effects of exposure to mutagenic chemicals on man himself. Additionally, compounds structurally similar to vinyl chloride must be studied to learn if they are genetically active in these tests. If they are, the effects of exposure to them must be evaluated. Currently NIEHS investigators are studying vinyl bromide, a compound structurally similar to vinyl chloride, which is used to make flame resistant fabric. Because this fabric can save lives NIEHS must determine whether vinyl bromide may be highly toxic and, therefore, unsafe to use without at least careful containment.

The difficulty with a situation such as the discovery that AF–2 is a potential mutagen and carcinogen is our inability to evaluate the immediate and long-term effects of such exposure directly on man. Although the genetic basis of many human diseases is well established, we are extremely limited in our ability to determine the immediate effects of genetic damage. And the long-term effects, such as an increase in cancer incidence, would not be expected to appear for at least 15 to 20 years. In such situations we may have the illusion of safety based on our inability to test rather than on sound scientific data. For this reason NIEHS scientists are giving high priority to the development of a capability to perform meaningful tests on man himself a short time after the exposure has occurred to determine and evaluate effects of inadvertent exposure to environmental compounds.

Noise

Other NIEHS research that may have an impact on a segment of our population began with research on noise. While developing techniques to evaluate how the ear handles acoustical information, one research team developed a device to impart complex signals, including speech, to the cochlea, the essential organ of hearing. This device may have important implications for people with certain kinds of hearing losses. No device, however, can greatly help people with severe sensory-neural losses resulting from exposure to excessive noise or certain drugs called ototoxic drugs. These losses are characterized by permanent destruction of a portion of the sensory cells and nerve endings.

By comparison with ordinary high-fidelity standards, conventional hearing aids are poor sound transmission devices. Further, because of the need for using a tiny acoustical diaphragm to generate sound in the hearing aid, great improvements are unlikely in the near future. To ask such a small diaphragm to perform acceptably over a wide amplitude and wide frequency range is asking it to perform the impossible and buck many of the laws governing sound generating equipment. These laws say that a fairly large vibrating object is required for efficient production of sound, particularly in the low frequencies.

In addition to the size problem, there are problems of feedback and squeal when the microphone and speaker are placed close together. Further, significant distortion is usually found when production of high-intensity, wide-frequency sound is attempted from small acoustic sources.

Doctors, called otologists, who specialize in ear problems have long thought that implanted devices might be capable of imparting sound directly to the inner ear by driving the ossicular chain, the small bones of the middle ear. They thought this could be done by placing a tiny direct-contact transducer at the ossicular chain. But until now no one has extensively examined the fidelity possible by using such devices.

NIEHS scientists have developed such a device, called a piezoelectric transducer. When in direct contact with the ossicular chain, it can impart highly defined signals to the cochlea. Experiments with research animals have shown this device produces the same order of fidelity as possible by the normal method of hearing.

2,4-D

Other studies underway at the Institute may help determine which marine species are safe for human consumption. These studies have focused on the way various marine species, including the dogfish shark, modify and dispose of the widely used herbidice 2,4-D (2,4-dichlorophenoxyacetic acid), a contaminant in the ocean. The dogfish shark makes an excellent model for studying 2,4-D as it has a simplier, but essentially similar, metabolic factory to man's. Its liver is less complex, yet the biochemical changes that take place in it seem to be comparable to those occurring in the human liver. In the NIEHS studies 2,4-D was found to be excreted much more slowly by dogfish shark than by the laboratory rat.

By showing how the body's handling of substances differs in various species we may be able to explain the variability in the period that environmental contaminants stay in marine species. This could be an important factor in determining which are safe for human consumption. We need to know which species store pollutants so human exposure can be prevented. Then we can avoid future problems like the sword fish-mercury scare of the 1970's.

Styrene Oxide

We may also be able to protect certain segments of our population from risk linked to exposure to specific pollutants if we can develop information on how the lung handles pollutants. The lung is the primary site of chemical toxicity, so the way it processes pollutants may play a significant role in the overall toxicity of chemicals.

To develop this information scientists at the Research Triangle Park Institute have been using a model system built around an isolated perfused lung. This system permits the study of rat and rabbit lungs outside the body while these organs are functioning normally for a time. It keeps the lung alive in the sense that it operates as it would in the body It also allows scientists to be sure that effects they are measuring are all happening in the lung. In this way we can understand the means by which the lung copes with inhaled substances.

One example of the use of this model system is NIEHS research on styrene oxide. This compound is a metabolite formed from styrene, one of the most widely used chemicals in the polymer industry. It is relatively safe to use and yet it is a

good model for studying the metabolism or processing of even more toxic chemicals, such as the polycyclic aromatic hydrocarbons, pollutants known to cause cancer.

In studies with styrene oxide scientists have shown that the amount of gultathione in the lung may be an important factor in whether styrene oxide is made less toxic, a process referred to as detoxication. When environmental agents enter the body, the first stage of processing they undergo leads to the formation of metabolites, some of which are more toxic to mammalian systems than the original contaminant. Some of these metabolites then may be detoxified by other systems in the body. Glutathione, a naturally-occurring substance in the body, is capable of making metabolites less toxic.

As glutathione concentrations in the lung decrease during the lung's continuing exposure to styrene oxide, NIEHS studies show swelling or edema. If the concentrations of glutathione is the limiting factor in the detoxication of styrene oxide, then it may be possible to protect workers exposed to this chemical by adding supplementary compounds to their diets that build glutathione.

Estimating Human Risk

The primary goal of all NIEHS research is to apply the findings to the human exposure situation and prevent disease. The public cannot afford to wait for clinical manifestations of diseases to appear before the search for potential causative agents begins. Because the latency period (time from initial exposure to effect) associated with such categories of disease as cancer and genetic disorders often ranges from ten years to two or more generations, a significant proportion of our population may be exposed to irreversible deleterious effects if we wait for sufficient human data to accumulate to conduct risk assessment.

Rather than waiting, decisions regarding acceptable levels of various environmental agents are being based on information derived from animal experiments, where cancer latency periods are reduced to intervals of 12 to 18 months and entire lifetimes are covered in a two to three year time span.

The procedure generally used to estimate risk associated with human exposure to a potential environmental carcinogen or cancer-causing agent usually begins with determining the carcinogenicity of the specified agent at relatively high doses in laboratory animals. The observed risk is then extrapolated or projected down to human exposure levels and equated to human risk by some conversion factor.

One of the major obstacles to developing realistic animal models for predicting human response is the problem of extrapolating to low dose levels, a procedure involving use of a mathematical model of the carcinogenesis process. Because two or more models may nearly coincide in the experimental dose range but yield widely divergent results in the actual range of human exposure, the model chosen for extrapolation is critical in determining the order of magnitude of the resulting estimate of human cancer risk.

Recently a team of NIEHS researchers has been examining probabilistic and mathematical models for extrapolation. They have emphasized models that specify possible biological mechanisms of carcinogenesis and have evaluated the importance of background incidence of disease and tumor induction in risk evaluation.

Their findings have been used to develop guidelines for selecting sample size and dose levels in animal carcinogenesis experiments. One of the design principles delineated in their effort indicates that increasing the number of animals beyond a certain level does not appear to bring about a proportional increase in the sensitivity of the test.

These efforts will continue so that the potential risk linked to exposure to environmental agents can be more realistically evaluated and so that human well-being can be protected.

National Eye Institute

research accomplishments

Fiscal year 1974 extramural

NEI-supported researchers at the Massachusetts Institute of Technology were able to determine in laboratory animals the mean size of the different proteins of the lens by measuring the spectrum of laser light scattered from the lens. Thus it is now possible to demonstrate the presence and size of the protein aggregates in the intact lens and to move toward studying the inception and progress of the development of cataract in humans, as well as the action at the molecular level of cataract-inducing or cataract-reversing biochemical reagents.

Researchers at Harvard found new evidence that the "orientation columns" of cells in the visual cortex (which are those cells specific to stimuli of a given position, shape, size, and direction of movement) are present at birth, but that early visual deprivation can affect the maturation and functioning of internal connections which are for the most part already formed. These studies also found that deprivation of sight in one eye shortly after birth causes the columns of cells specific to that eye to shrink in width while there is an increase in the width of columns receiving input from the remaining eye. Such findings demonstrate the flexibility and plasticity of the visual nervous system and the anatomical and functional basis for visual responses which have heretofore only been demonstrated through behavioral studies.

NEI-supported investigators at the University of Florida, Gainesville, developed a medium which permits the storage of corneal tissue in healthy living condition considerably longer than was previously possible when the cornea was stored as part of a refrigerated eye. These techniques have extended the survival of the corneal endothelium and have made possible longer-term storage for eye bank tissue. Graft transplant failures, which had been thought to be due to the death of some tissues, have been minimized by the use of this technique which also reduces the liklihood of corneal transplant rejection by washing out antigens which may be foreign to the recipient.

Researchers at Johns Hopkins University developed a method of simultaneously but separately photographing the retinal and choroidal circulations by using a multispectral fundus camera after a single intravenous injection of fluorescein and indocyanin green dyes. Thus investigators can obtain angiograms which provide information about the blood flow in retinal vessels, and in choroidal arteries, veins, and capillaries. Routine observations of blood flow in retinal and choroidal circulatory systems will help in understanding the pathogenesis of vascular diseases of the eye and permit eary diagnosis.

Soft, hydrophilic contact lenses, developed over the last 10 years, have recently been approved by the Food and Drug Administration for use in the treatment of a blistering condition of the cornea, bullous keratopathy. FDA approval came after research, much of which was supported by the National Eye Institute, demonstrated that the soft lens can serve as a protective bandage for the diseased cornea, allowing it to heal while protecting it from the abrasive action of the eyelids. Approval of soft lenses for treating other corneal conditions which are difficult to manage by conventional means is anticipated within the near future. This therapeutic use of a device originally intended as an alternative for those who had trouble adjusting to hard contact lenses for correction of refractive errors represents a major breakthrough in the management of painful and disabling corneal conditions.

Fiscal year 1974 intramural

NEI scientists developed an animal model suitable for studying the effects of chronic elevation of intraocular pressure. The researchers induced an experimental glaucoma in the eyes of normal rhesus monkeys by repeated use of the laser on an area in the recess of the anterior chamber angle. This model will provide a tool for studying why and how glaucoma causes visual loss. It will allow investigations that cannot be performed in man but are necessary if we are to understand the effects of glaucoma, and it will permit comparison of retinal optic nerve function in the glaucoma eyes to those in the control eyes.

New surgical instruments, developed with NEI support, are now being used to simplify and extend the range of treatment for complicated forms of retinal detachment and for diseases of the vitreous, the normally transparent gel that fills the center of the eye. These developments have made vitrectomy one of the most exciting new fields of eye surgery, and studies are now under way to evaluate its potential for restoring sight to people who would otherwise remain blind.

Other NEI scientists have found that as new cortical fibers are laid down in the lens, the γ-crystallin (protein) of larger molecular dimensions predominated, whereas in the younger lens the lighter form is found in greater abundance. This age-related change in the γ-crystallin is one of the first examples of the effect of aging on lens proteins. This is important because an understanding of the basic chemistry and physiology of the lens is needed to understand the cataractous process.

Sugar cataracts in mice with experimentally induced diabetes were studied in order to explore possible means by which cataracts can be prevented. The major finding of this study has been the continuing evidence supporting the concept that the enzyme aldose reductase is involved in initiating the formation of sugar

cataracts. This enzyme appears to be the common mechanism by which the sequence of events leading to the development of diabetic, galactosemic, and xylosemic cataracts is initiated. An active inhibitor of aldose reductase has recently been shown to prevent cataractous changes in cultured lenses exposed to high concentrations of galactose. Improved methods of delivery of the aldose reductase inhibitor by topical application must now be achieved if this procedure to control cataract formation is to be effective.

Fiscal year 1973 Extramural

NEI-supported researchers at Johns Hopkins University found that retrolental fibroplasia can occur as a congenital defect. Their findings indicate that factors other than exogenously induced hyperoxia in the nursery may produce the typical proliferative lesions of retrolental fibroplasia.

Investigators at the Retina Foundation in Boston developed a nonabsorbable scleral implant made of silicone, which can be inflated or deflated at will during surgical procedure and for several weeks postoperatively for treatment of difficult cases of retinal detachment.

DIVISION OF RESEARCH RESOURCES (DRR), NIH

A. Ten significant research developments supported by DRR over the past five years:

1. A new virus has been discovered at the Delta Primate Research Center in Louisiana which bears a close resemblence to the chickenpox virus—varicella.

The discovery of the new virus, now labeled Delta Herpesvirus (DHV), may eventually lead to the development of a chickenpox vaccine to conquer one of the few remaining uncontrolled childhood diseases.

One of the major obstacles to developing a vaccine against the chickenpox virus has been the lack of an experimental animal for laboratory studies. The solution to the problem is now in sight with the surfacing of this chickenpox-like disease in patas monkeys at the Center, which is supported by NIH's Division of Research Resources.

Chickenpox is the most common reportable disease of children in the United States. During the first half of 1975, over 110,000 cases were reported, and the actual number could be much higher. It is an acute communicable disease, principally of young children, caused by a virus, and marked by slight fever and an eruption of small spotted blisters. They rarely become filled with pus, but dry up; only occasionally are they followed by scars. The duration of the disease is about a week, during which time it runs a very mild course.

Few people reach adult life without becoming infected by chickenpox. Although usually benign, it can result in more serious disease, such as encephalitis in children, or pneumonia in adults. It is also a serious problem in persons with hematopoeitic and lymphatic malignancies such as leukemia, Hodgkins disease, and lymphoma. Patients who have inadequate immunological defenses are particularly vulnerable. Under these conditions, the disease is often fatal.

The DHV virus caused two outbreaks in patas monkeys. The disease resembled a more severe form of chickenpox. Antigenically, the virus closely resembles, or is identical to, varicella virus. Like varicella, DHV is a cell-associated virus which means it is difficult to recover large quantities of the virus free from the cells in which it grows. Other biological features, however, make it distinguishable from the human chickenpox virus.

The disease produced by DHV in patas monkeys can be termed as a monkey form of chickenpox and will be useful as a model of human varicella. Because DHV stimulates antibody that affects varicella virus, it may have some potential usefulness as a vaccine against chickenpox. Any anti-varicella vaccines which will be developed can be tested against the experimental disease in monkeys.

This varicella-like disease of monkeys can also be used to evaluate antiviral drugs for their potential in preventing or curing varicella infections. Some laboratory evidence suggests that DHV may be used in tests to measure human immunity to chickenpox.

Virologist Ambhan Felsenfeld, M.D., heads the group currently engaged in transmission studies of the new virus. The Delta virologists are also attempting to determine how DHV relates to other known viruses. In addition, they are also delving into the relationship of shingles (herpes zoster) to chickenpox. In man, the same virus causes both diseases. All people who get shingles have had chickenpox at one time or other.

The development of the patas monkey as the suitable laboratory animal model will enable researchers to study the disease in detail, perfect methods for laboratory growth of the virus, and attempt to perfect a successful vaccine.

2. The development of the nine-banded armadillo as the key laboratory animal model for leprosy research (Hansen's disease) has contributed significantly to recent breakthroughs in skin testing for human leprosy.

Leprosy affects an estimated 15 million persons in the world with heavy concentration in tropical zones. The skin test is used in classifying the type of leprosy in afflicted patients.

Researchers at the Gulf South Research Institute in Louisiana report that lepromin prepared from armadillo bacilli comparable in quality to lepromin prepared from human bacilli. Human bacilli is limited and is not always available.

The sole source of significant amounts of armadillo leprosy bacilli, Gulf South has recently been designated as a collaborative laboratory of the World Health Organization.

Dr. Eleanor E. Storrs, director of the Department of Biochemistry, has been the prime motivator of armadillo research and colony development—now the largest in the world—with support from NIH's Division of Research Resources.

The low skin and body temperature (about 90 degrees F.) of the armadillo is one of the major factors which makes the football-shaped animal suitable for leprosy research since the leprosy bacterium requires a low temperature for optimum growth.

The armadillo's span of life is from 12 to 15 years, giving researchers a longer period to study the progressive form of the disease. In man, the estimated leprosy incubation period averages three to five years. It is now known that the leprosy organism invades the bone marrow and lungs in the armadillo.

Medical scientists previously had developed something resembling progressive leprosy in mice following removal of the thymus gland and destruction of bone marrow by X-ray. However, mice live only for about two years, and there was a strong need for an unaltered animal with longer life expectancy.

Successful innoculation of lepromatoid leprosy in the armadillo was reported in 1971 as the result of collaborative study by Dr. Storrs and Dr. Waldemar F. Kircheimer of the U.S. Public Health Service Hospital at Carville, La. Gulf South researchers have since found that leprosy-induced armadillos have extremely high bacilli levels. A single armadillo has yielded sufficient bacilli to prepare 1,500 liters of standard lepromin—enough for 15 million lepromin skin tests.

The nine-banded armadillo is encased in an armor-like plate with nine bands, has a large snout, large ears, and abounds in southern and southwestern states of the country. The female armadillo regularly produces identical quadruplets of the same sex.

The unusual physiological characteristics of the armadillo lend themselves to several other important areas of biomedical research. The animal is apparently the first laboratory model found for studies of *Buruli ulcerans* (a type of skin ulcer). They have also found the armadillo to be a natural host for Chagas disease (a parasitic disease prevalent in South America), and a wide variety of rickettsial diseases.

Current collaborative programs with use of the armadillo include the establishment of a World Lepromin Bank, and the development of a vaccine against leprosy.

3. Biomedical research on thymic function and cataract formation in the human body may well be advanced due to the development of a dimunitive South American rodent—the degu—as a laboratory animal model.

Two unusual physiological quirks in this particular species of rodent have given indication that the degu may prove to be one of the most useful laboratory animals yet developed in these two important health research areas. The animals are born with two anatomically separate thymus glands. In addition, upon reaching adulthood, a good percentage of the animals develop cataracts.

Originally housed at the Massachusetts Institute of Technology, the colony is now flourishing at the University of Vermont in Burlington. Dr. David K. Boraker, immunologist, is in charge of the 500-animal colony of degus, the largest in the United States. In early 1973, NIH's Division of Research Resources through its Animal Resources Branch, awarded a grant to Dr. Boraker for the development of the pedigreed colony for biological and biomedical experimentation.

The double thymus phenomenon is of particular interest to immunologists who are attempting to decipher the function of the thymus, the "master" organ which in early life sets up the immune defense mechanisms for the body.

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In comparison with the traditional experimental animal—the mouse—immunologists at the University of Vermont feel that the anatomical location of the double thymus in the degu makes it far more accessible for thymic research.

The thymus in the human and in most mammals is a single structure located in the upper chest cavity. The thymus is of fundamental importance in the development of the immune system of the body. It is primarily important in establishing the body defense mechanisms in late fetal life and early life after birth—up to about 14 years of age in the human. After this, the organ usually undergoes fatty metamorphosis and atrophy (decreasing in size and wasting away).

The degu is consistently born with a cervical thymus (located in the neck), and a mediastinal thymus (located in the upper chest cavity). The cervical thymus can be removed quite easily without harming the animal.

Sometimes referred to as a trumpet-tailed rat, the degu weighs about 7 grams at birth and grows up to nearly 300 grams in adult life. Its life cycle span runs from three to five years. With a breeding cycle yielding two litters per year, an average of five newborns are produced at the end of the 90-day gestation period.

The discovery of "sugar cataracts" in adult degus was of vital interest to Dr. Jin H. Kinoshita, chief of Laboratory Vision Research, National Eye Institute. The University of Vermont researchers, working in collaboration with Dr. Kinoshita's group, have found that these degus apparently have a metabolic disorder in sugar metabolism which results in the precipitation of cataracts. The possibility exists that this high blood sugar level found in the degu may be associated with a physiological condition analogous to diabetes.

This development has now led to the possibility of the establishment of a separate degu colony at the University of Vermont of a genetically defined strain with high incidence of cataracts for specific use of the National Eye Institute.

4. The possibility of dissolving gallstones in the human body is closer now than ever before due to the research being conducted at the Mayo Clinic. Fifteen years of concentrated research on bile acids by Dr. Alan F. Hofmann, Associate Director of the Gastroenterology Unit, may come to fruition as the feasibility of using a pharmacological substance to dissolve gallstones emerges.

The compound, chenodeoxycholic acid (chenic acid) is a natural bile acid in man. Oral dosage of chenic acid to effect bile acid balance in the body may ultimately be commonly prescribed as nonsurgical therapy for cholesterol gallstones, says Dr. Hofmann. His work with Dr. Johnson L. Thistle, another Mayo Clinic researcher, may eliminate the necessity of high-risk patients having to undergo cholecystectomies (gallstone operations).

A controlled clinical trial, utilizing chenic acid dosage, was conducted with 30 men and 26 women at the Mayo General Clinical Research Center. After six months, more than half of the patients showed reduction in gallstone size. Subsequent X-rays revealed the gallstones had disappeared in 13 of the patients.

Gallstones are caused by a cholesterol oversaturation of the bile in the human body. Cholesterol is kept in solution by two other components of the bile, lecithin and bile acids. When the ratio of cholesterol to lecithin and bile acids is too great, gallstones form. If the concentration of bile acids can be increased, the cholesterol will again become soluble and the gallstones will dissolve.

The chenic acid dosage technique attempts to achieve proper equilibrium between the components of the bile. Since Dr. Hofmann feels that factors determining the saturation of bile are still not thoroughly understood, he and his co-workers are continually conducting intensive investigations at Mayo Clinic.

Dr. Hofmann has been a proponent of chenic acid therapy since his initial studies as a research associate at Rockefeller Institute. He is internationally recognized as a leader in this area and was chairman of a workshop on chenic acid therapy of gallstones held in Freiburg, West Germany in 1973.

The concept of cholesterol gallstone dissolution by oral dosage of chenic acid is gathering momentum in clinical research circles. Going deeper into controlled toxicity studies of chenic acid dosage, a national cooperative trial has been funded by the National Institute of Arthritis, Metabolism, and Digestive Diseases which calls for the establishment of ten gallstone study centers throughout the country. Approximately 100 patients will be treated in each center. Dr. Leslie J. Shoenfield, Director of Gastroenterology at the Cedars-Sinai Medical Center in Los Angeles, has been appointed coordinator of this program.

Dr. Hofmann firmly believes that the medical conquest of cholesterol gallstones is fast approaching. "In the future, gallstones should be detected much earlier because of improvements in ultrasound techniques," he says. "High risk individuals may be detected by studies on bile acid metabolism before the patient

gets gallstones, and prophylatic therapy initiated. New techniques will be developed for *in situ* dissolution of common duct stones."

5. A dietary supplement in the form of keto-analogues of essential amino acids can postpone the need for kidney dialysis in some cases, and lengthen the period between dialysis or temporarily take patients off dialysis in other cases, it has been domonstrated by clinical researchers at the Johns Hopkins General Clinical Research Center (GCRC).

Clinical trials conducted by Drs. Mackenzie Walser and William E. Mitch at the DRR-supported Inpatient and Outpatient GCRCs have established that the provision of a dietary supplement in the form of keto acids decreases the load of nitrogenous waste required for excretion by the kidney.

The researchers have determined that these substances could serve as building blocks for protein, and that under these conditions there is a marked conservation of nitrogen by the body.

It is estimated that approximately 60,000 people die each year in the United States with renal failure. Most of these could be helped by hemodialysis (an artificial means of removing waste from the blood normally removed by the kidneys when they are functioning properly).

At present, there are about 16,000 patients receiving dialysis, which is expensive (approximately $125 per treatment), inconvenient, and time-consuming.

Because metabolism of nitrogen in the body begins with dietary intake of protein and ends up with renal excretion of urea, the Johns Hopkins scientists have concentrated their efforts in improving the efficiency of the transamination process in the body. Transamination is actually a recycling process wherein nitrogen (in liver and muscle) is transferred from nonessential to essential amino acids, and also adjusts levels of individual amino acids to tissue needs.

This treatment in most cases has postponed the need for dialysis by renal patients for months, the clinical scientists report, by reducing urea production—and in some cases by slowing down the progression of the renal deterioration.

In a most recent GCRC outpatient study, seven renal failure cases were treated with the keto acid diet. One of the seven had been on dialysis twice a week for five months. The other six were considered prime candidates for immediate dialysis.

By subsequent keto acid therapy, six of the patients were maintained for an average period of six months before dialysis had to be instituted or reinstituted. The seventh patient remains completely off dialysis after more than one year.

None of the group developed any of the usual signs of renal incompetence or uremic poisoning, including peripheral neuropathy, premature atherosclerosis, renal osteodystrophy, or lowered bone density. Three of the seven had shown reduced nerve conduction velocity prior to treatment. This improved during keto acid therapy in two of the three. Three patients also showed a reduction of previous high plasma triglycerides to values within the normal range.

The keto acids used in these clinical tests were actually synthesized at the Johns Hopkins University School of Medicine. It is speculated that the cost of this production will be greatly reduced when the pharmaceutical and chemical industries gear up for keto acid distribution.

6. The treatment of patients with Parkinson's disease was revolutionized in the late 1960s by the introduction of L-dopa, an amino acid which calms the tremor and improves the mobility of these individuals, usually sparing them from brain surgery. Much of the work in developing this drug was performed on a GCRC. However, in some patients, L-dopa affords only short-term relief. GCRCs have continued to test new drugs in this disease, some of which have been particularly beneficial in extending the extraordinary benefits of L-dopa into "permanent" control.

7. A new cell reconstruction technique, enabling cell biologists to mass produce millions of cells in different combinations of nuclei and cytoplasms, has been developed at the University of Colorado (CU) at Boulder.

The new technique, perfected by CU scientists at the Department of Molecular, Cellular, and Developmental Biology, opens up many areas of research, including prospects for generating haploid cells (cells with only half the number of chromosomes in body cells), and for investigating the ability of cells to differentiate into nerve cells, muscle cells, and the rest of the specialized types of cells which make up man and other multicellular forms.

Laboratories throughout the United States have now adopted the new technique and are using it for their studies.

The CU method of cell reconstruction was evolved with the aid of the million-volt electron microscope which is supported by DRR. This microscope at CU is one of the only two existing million-volt electron microscopes in the country being

used for biomedical research. The other one is located at the University of Wisconsin.

The great penetrating power of the million-volt electron beams and the reduced beam damage permits the investigator to obtain sharp 3-D images of how cells are constructed. The viewing of whole intact cells with the various subcellular components clearly resolved is now possible. For example, CU scientists report that they have found large molecules within the nerve-muscle membrane system of mice and chickens never previously seen by other researchers.

Drs. Keith R. Porter, George Veomett, David M. Prescott, and Jerry Shay comprised the research team which successfully developed the new cell reconstruction technique.

Using a special strain of mouse cells (L929), the CU scientists first treat the cell with a compound called *cytochalasin B*, which is known to give the cell nucleus freedom to move to the outer edge of the cells. At this point, only low centrifugal force is needed to pull the nucleus out of the cell and break the thin thread between the nucleus and the cytoplasm. Thus is formed the karyoplast (a body containing the nucleus and a small amount of cytoplasm), and the cytoplast (a body containing the remainder of the cytoplasm).

Two such treatments on different types of cells provide scientists with karyoplasts from one set of mouse cells and cytoplasts from another set. When these two parts of the cells are exposed to an inactive virus, they re-fuse, and a mass of hybrid cells is produced.

Testing the success of the fusion is achieved by feeding a radioactive substance to one group of cells in culture, and tiny latex spheres (a plastic material similar to that added to latex paint) to another set of culture cells.

The radioactive substance is known to be deposited in the nucleus, and the large latex spheres to be taken up by the cytoplasm. When most of the resulting hybrid cells had both, CU scientists knew that the fusion had been successful. The resulting cells remain alive and continue to divide, thus proving that they are not impaired by the process.

8. The Stanford University Medical Experimental Computer (SUMEX-AIM) has been established to provide the first national shared computer facility for research on artificial intelligence in medicine.

Directed by Dr. Joshua Lederberg, professor and chairman of the Department of Genetics, SUMEX-AIM is an innovative effort to help biomedical scientists meet today's research requirements and to explore computer applications in many health fields, ranging from basic research to clinical diagnosis and choice of therapy.

At present, SUMEX-AIM consists of a powerful PDP–10 computer available to approved users throughout the United States over a computer communication network on a time-shared basis.

Artificial intelligence is a part of computer science concerned with the symbol-manipulation processes that produce intelligent action. Rather than employing the digital computer as merely a number calculator, scientists in this field utilize the computer to reach decisions and solve problems through symbolic analysis and reasoning.

Initial applications of this approach to medicine are being actively pursued in medical diagnosis, planning of therapy, and the interpretation of data from advanced chemical structure studies.

Some major artificial intelligence projects currently in progress are:

Casnet

A group of computer scientists, led by Dr. Casimir Kulikowski of Rutgers University, is developing computer-based consultation systems for diseases of the eye (initially glaucoma) in collaboration with Dr. Aran Safir, ophthalmologist, at the Mount Sinai School of Medicine. The computer system, which includes an elaborate pathophysiological model of glaucoma, is being tested in eye centers at the Mount Sinai Hospital and Medical Center, New York; Washington University, St. Louis; and the Johns Hopkins University Hospital, Baltimore.

Dialog

A diagnostic project under the direction of Dr. Harry Pople and Dr. Jack Myers of the University of Pittsburgh, the DIALOG system deals with the general problem of diagnosis in internal medicine. It currently accesses a medical data base encompassing approximately 50 percent of the major diseases in internal medicine.

Mycin

This is a computer-based consultation-in-clinical-therapeutics project, directed by Dr. Stanley Cohen, associate professor and head of the Division of Clinical Pharmacology at Stanford University. MYCIN attempts to model the decision processes of medical experts in arriving at the selection of therapy for patients with bacterial infections.

Dendral

This program is aimed at assisting the biochemist in interpreting molecular structures from mass spectral and other chemical information. It is conducted at Stanford University under the leadership of Drs. Joshua Lederberg, Edward Feigenbaum, and Carl Djerassi.

X-Ray crystallography

Protein crystallographers Drs. Joseph Kraut and Stephen Freer at the University of California, San Diego, are using the SUMEX–AIM facility as the central resource for programs, data, and other information of common interest. The general objective of the program is to apply problem-solving techniques, emerging from artificial research, to determine the three-dimensional structure of proteins.

9. One of the more significant developments funded by DRR is the development of research and research training capabilities at *minority institutions* such as the Atlanta University Center Corporation in Atlanta, Georgia. As a result of funding through the Minority Biomedical Support Program, that group of five institutions has been able to establish and expand a strong research program unheard of and unqualed in any minority institution during such a short period of time (three years). The following table illustrates the effect of the MBS Program at the Atlanta University Center Corporation:

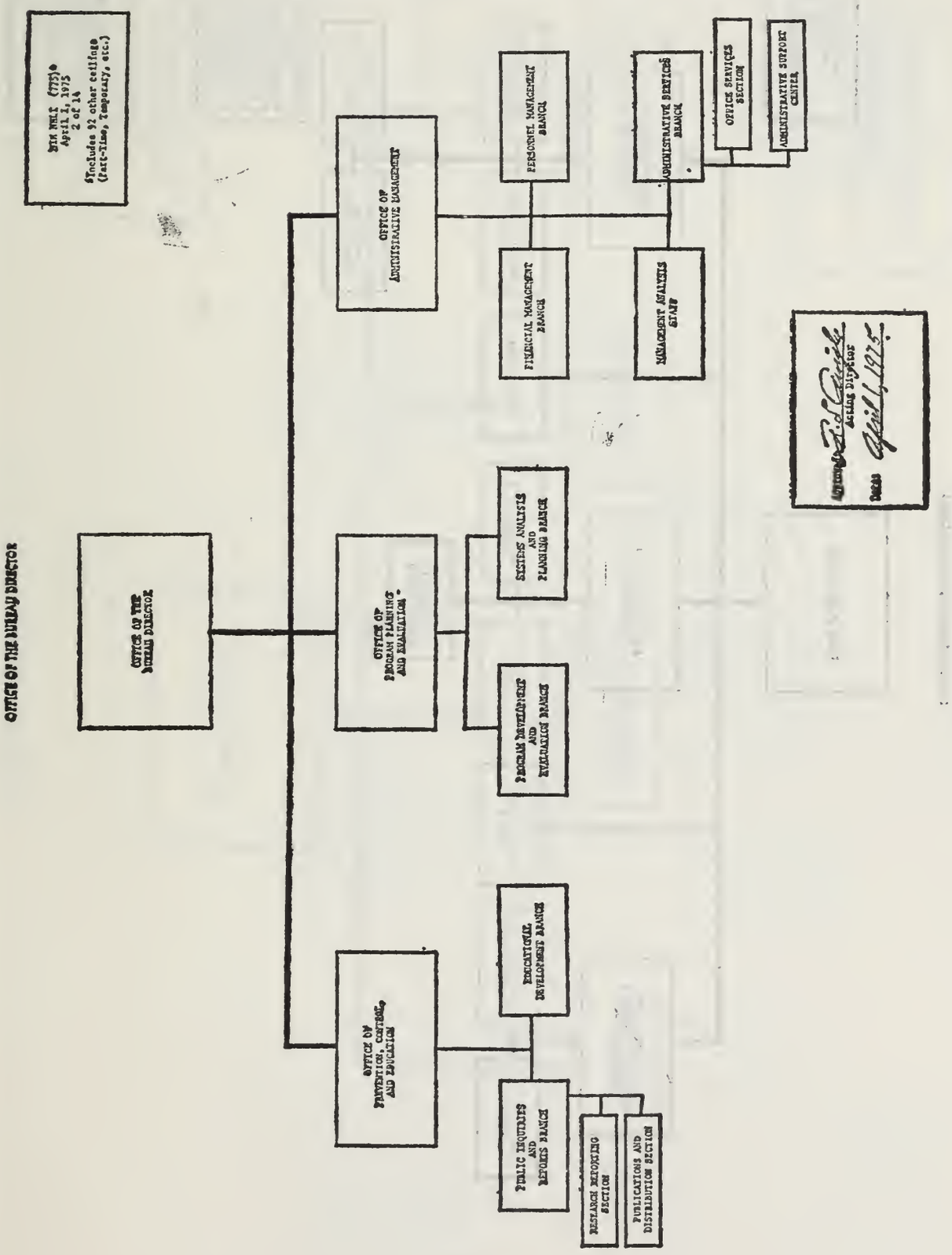
Year	Number of publications	Number of students—Ph. D. level
1972	5	2
1973	12	10
1974	31	20

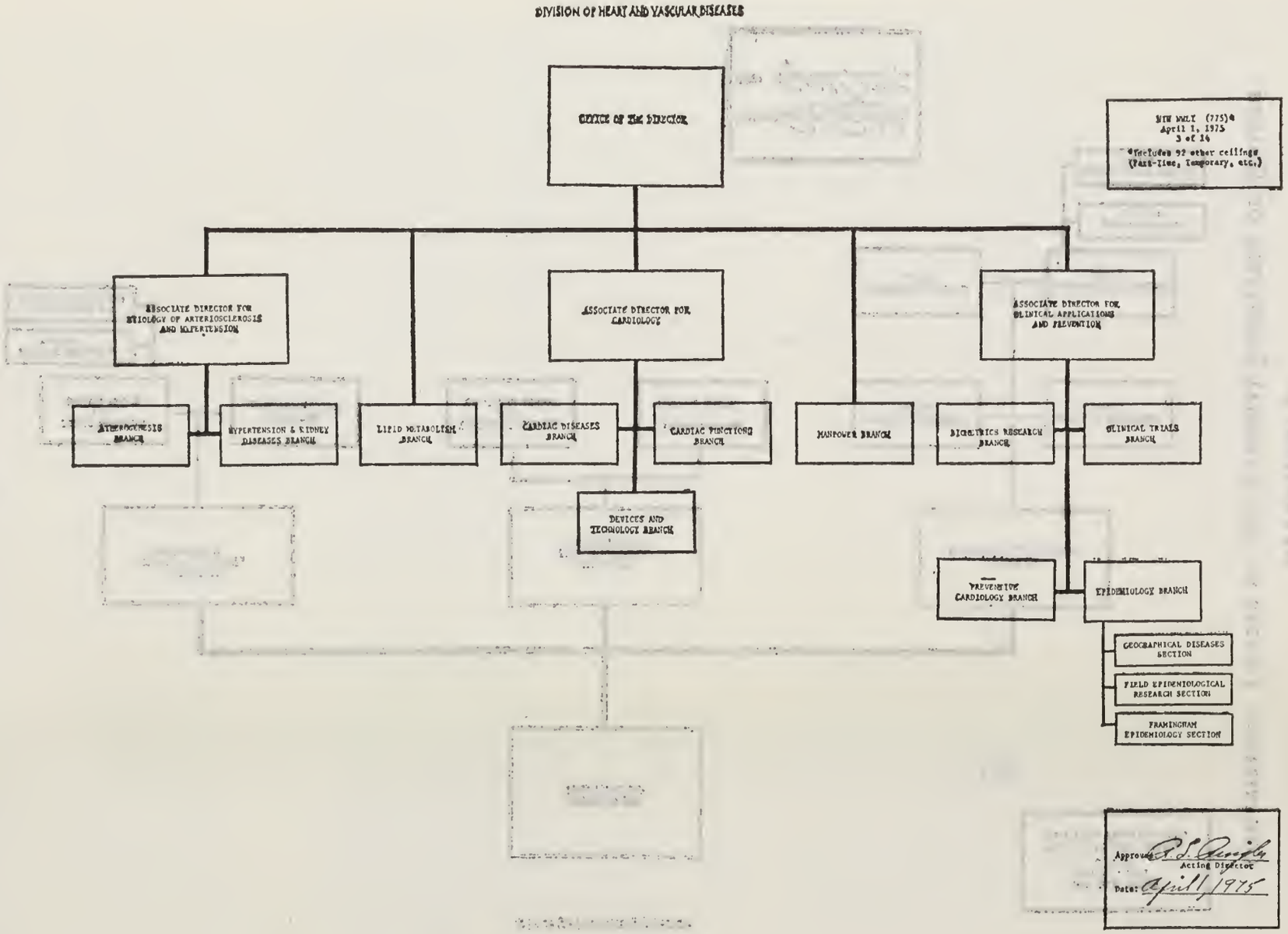
The MBS grant was begun in June 1972. There are presently 41 faculty investigators participating in the program, whereas in 1972 there were about 10 faculty actively engaged in research. In 1972, they started out with 16 student trainees and in 1975, there are 77 participating.

10. Preferential Cerebral Hypothermic Perfusion was developed at Montefiore Hospital Association of Western Pennsylvania, Pittsburgh through the use of General Research Support funds. This procedure permits extensive brain surgery under hypothermia without total body cooling. It has been used in conjunction with elective cardiac arrest for cerebro-vascular surgery. Studies are continuing to determine its value in open heart surgery.

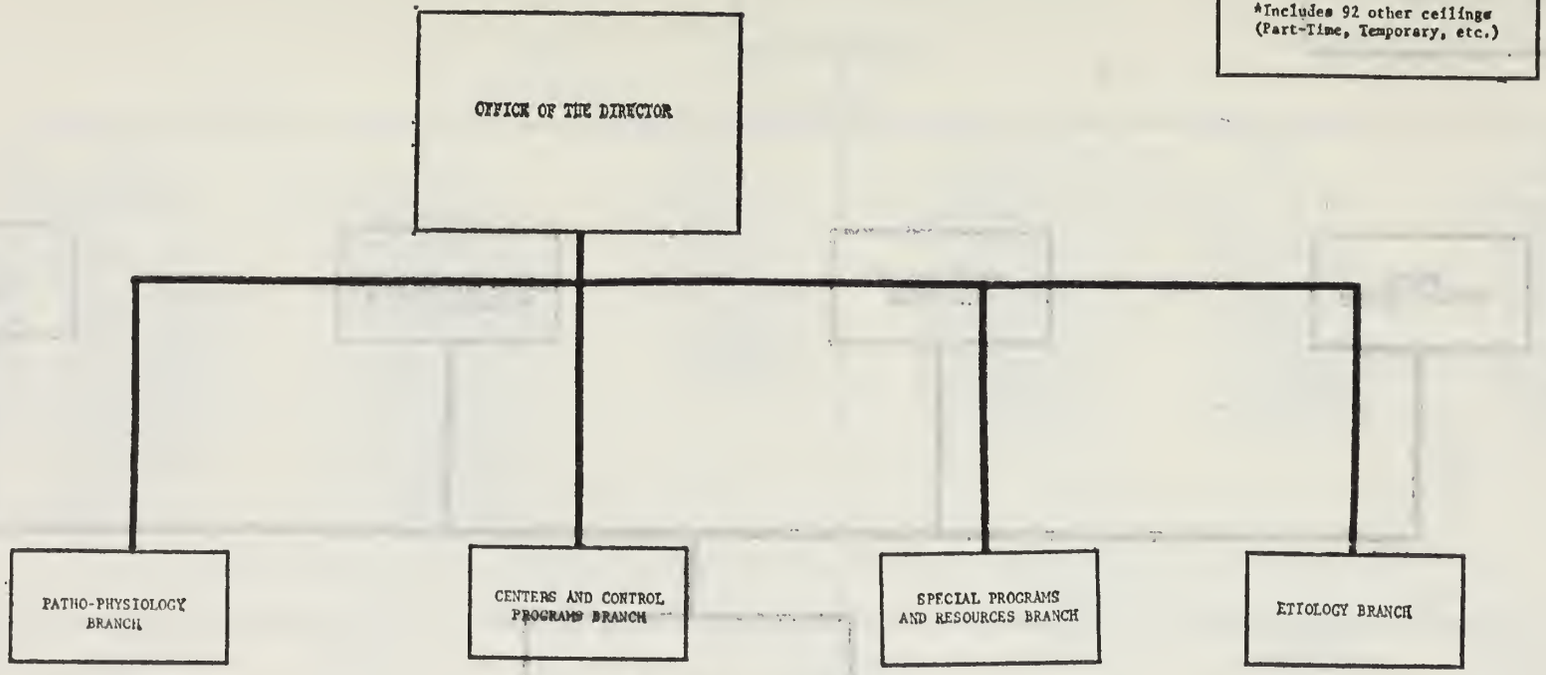
APPENDIX 2

Organization Charts of the National Institutes of Health




DIVISION OF HEART AND VASCULAR DISEASES
OFFICE OF THE DIRECTOR
NIH WAIT (775)*
April 1, 1975
3 of 14
*Includes 92 other ceilings (Part-Time, Temporary, etc.)
ASSOCIATE DIRECTOR FOR ETIOLOGY OF ARTERIOSCLEROSIS AND HYPERTENSION
ASSOCIATE DIRECTOR FOR CARDIOLOGY
ASSOCIATE DIRECTOR FOR CLINICAL APPLICATIONS AND PREVENTION
ATHEROGENESIS BRANCH
HYPERTENSION & KIDNEY DISEASES BRANCH
LIPID METABOLISM BRANCH
CARDIAC DISEASES BRANCH
CARDIAC FUNCTION BRANCH
MANPOWER BRANCH
BIOMETRICS RESEARCH BRANCH
CLINICAL TRIALS BRANCH
DEVICES AND TECHNOLOGY BRANCH
PREVENTIVE CARDIOLOGY BRANCH
EPIDEMIOLOGY BRANCH
GEOGRAPHICAL DISEASES SECTION
FIELD EPIDEMIOLOGICAL RESEARCH SECTION
FRAMINGHAM EPIDEMIOLOGY SECTION
Approved: R. S. Ruoff
Acting Director
Date: April 1, 1975

DIVISION OF LUNG DISEASES



NIH NHLI (775)*
April 1, 1975
4 of 14

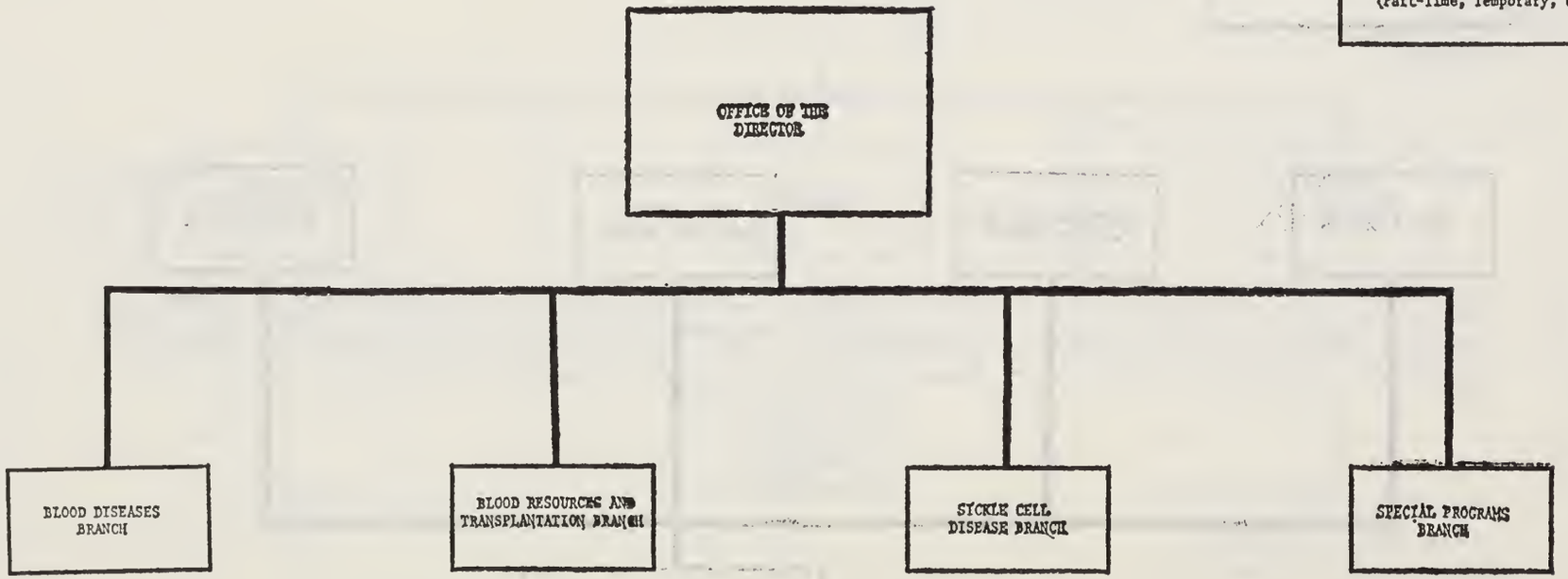
*Includes 92 other ceilings (Part-Time, Temporary, etc.)

Approved: R. S. Gromby
Acting Director

Date: April 4, 1975

DIVISION OF BLOOD DISEASES AND RESOURCES

NIH NHLI (775)*
April 1, 1975
5 of 14
*Includes 92 other ceilings
(Part-Time, Temporary, etc.)

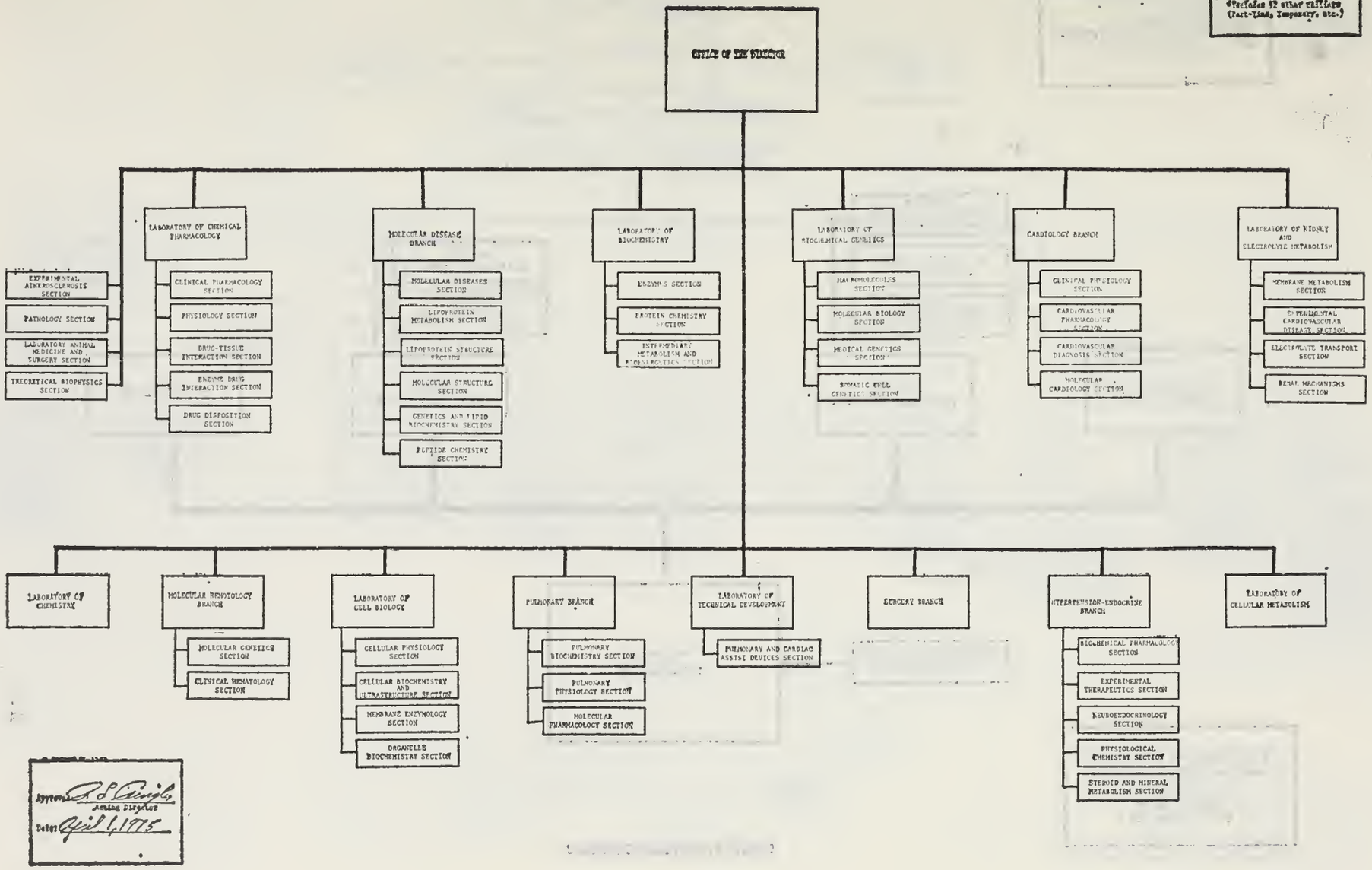


Approved: R. S. Ravnikar
Acting Director

Date: April 1, 1975

DIVISION OF INTRAMURAL RESEARCH

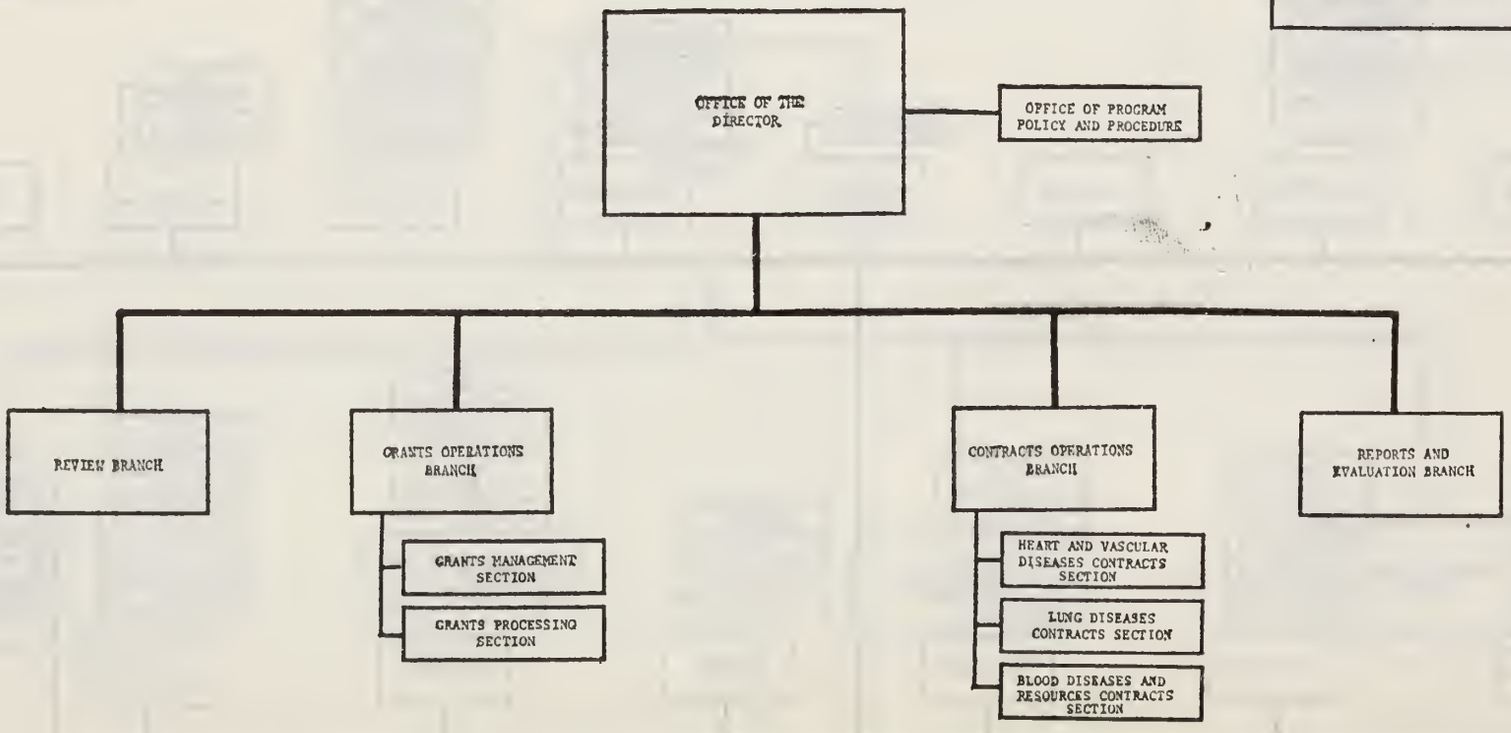
NIH 1MEE (7/75)
April 1, 1975
6 of 14
*Includes 52 other staffing
(Part-Time, Temporary, etc.)



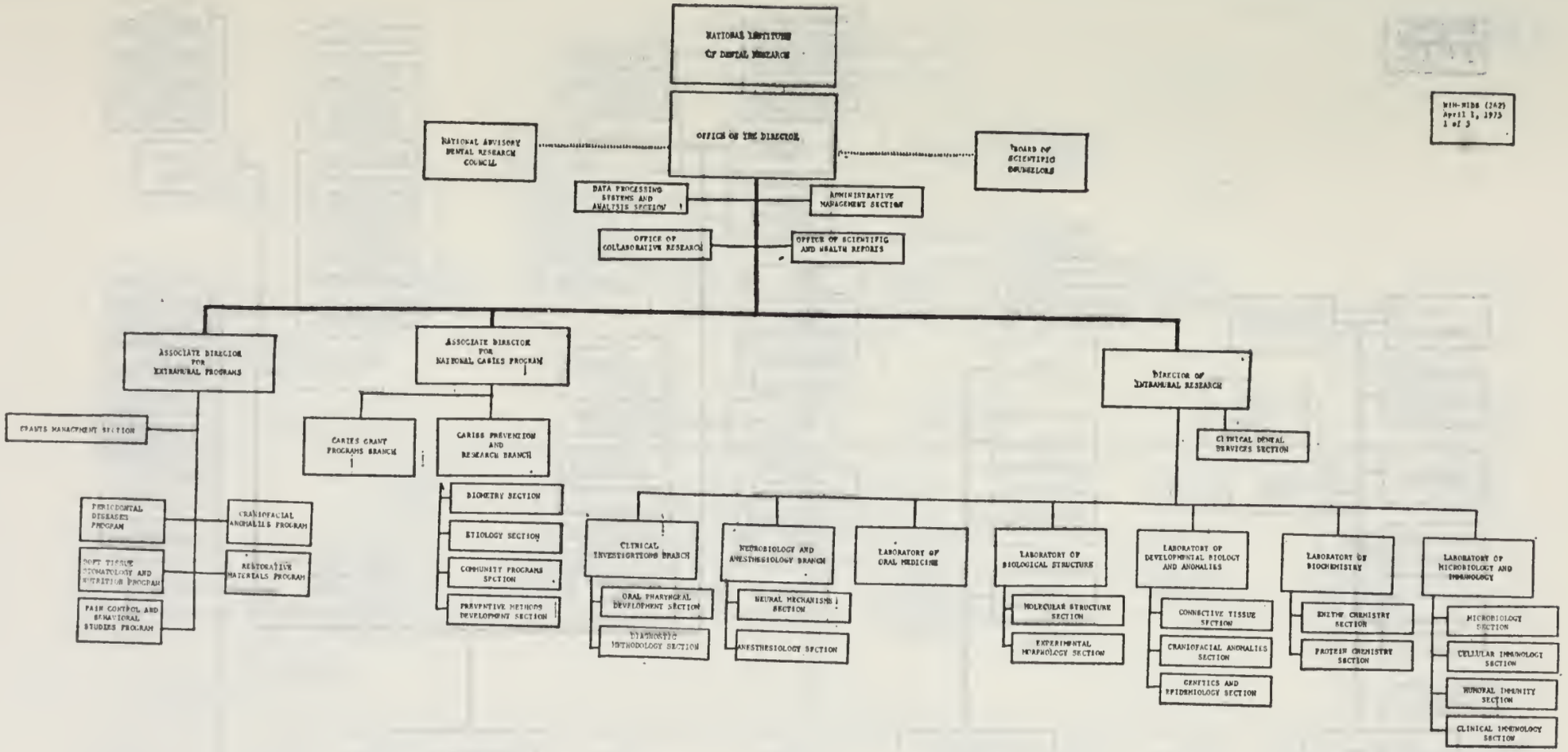
Approved: D. S. Gingle
Acting Director
Date: April 1, 1975

DIVISION OF EXTRAMURAL AFFAIRS

NIH NHLI (775)*
April 1, 1975
7 of 14
*Includes 92 other ceilings
(Part-Time, Temporary, etc.)

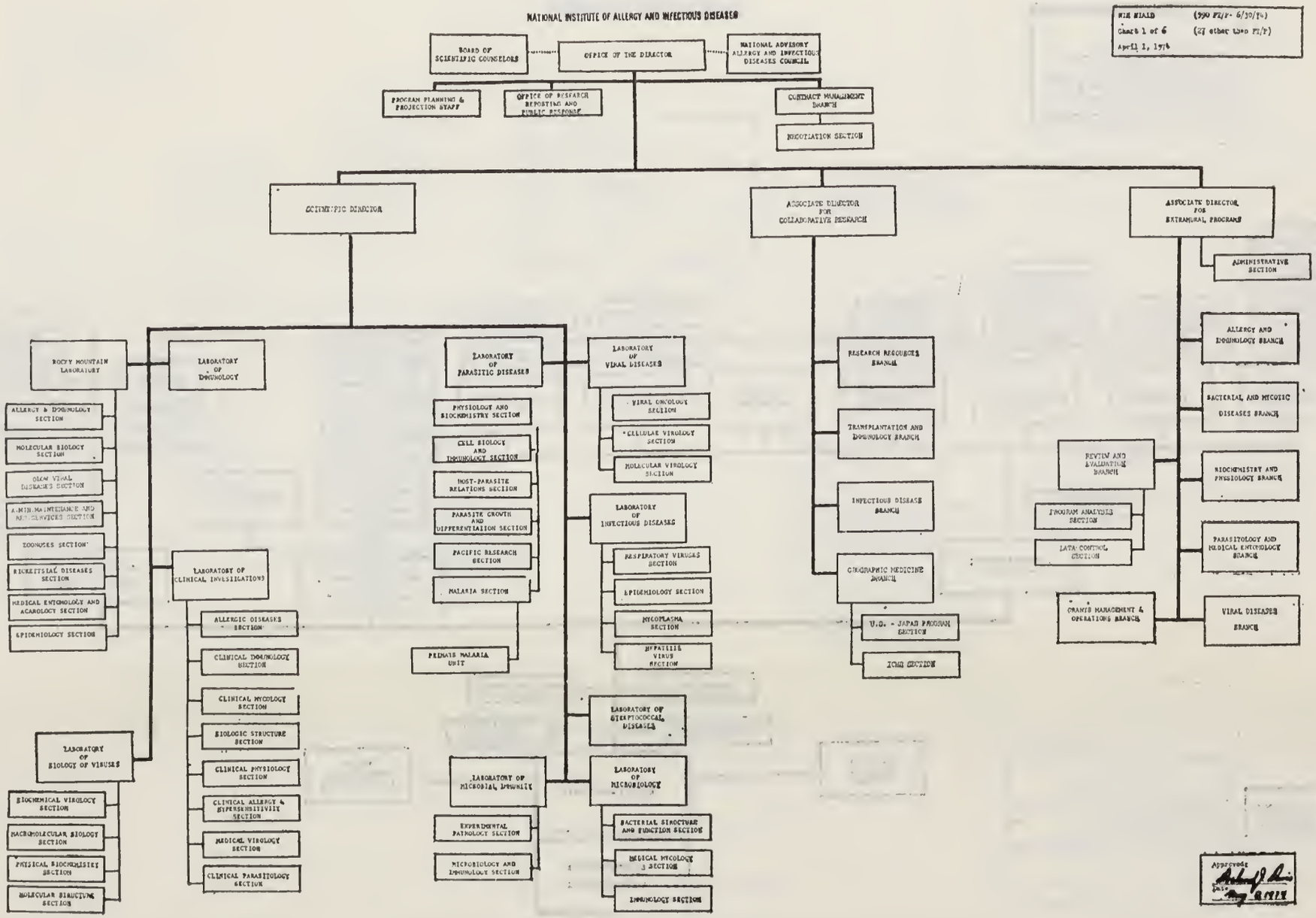


Approved: R. S. Gerstley
Acting Director
Date: April 1, 1975



NIH-NIDR (242)
April 1, 1973
1 of 3

Approved: [signature]
Date: 4 April 73


NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
NIH NIAID (990 FY/F- 6/30/74)
Chart 1 of 6 (27 other than FY/F)
April 1, 1974
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OFFICE OF RESEARCH REPORTING AND PUBLIC RESPONSE
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ASSOCIATE DIRECTOR FOR COLLABORATIVE RESEARCH
ASSOCIATE DIRECTOR FOR EXTRAMURAL PROGRAMS
ADMINISTRATIVE SECTION
ROCKY MOUNTAIN LABORATORY
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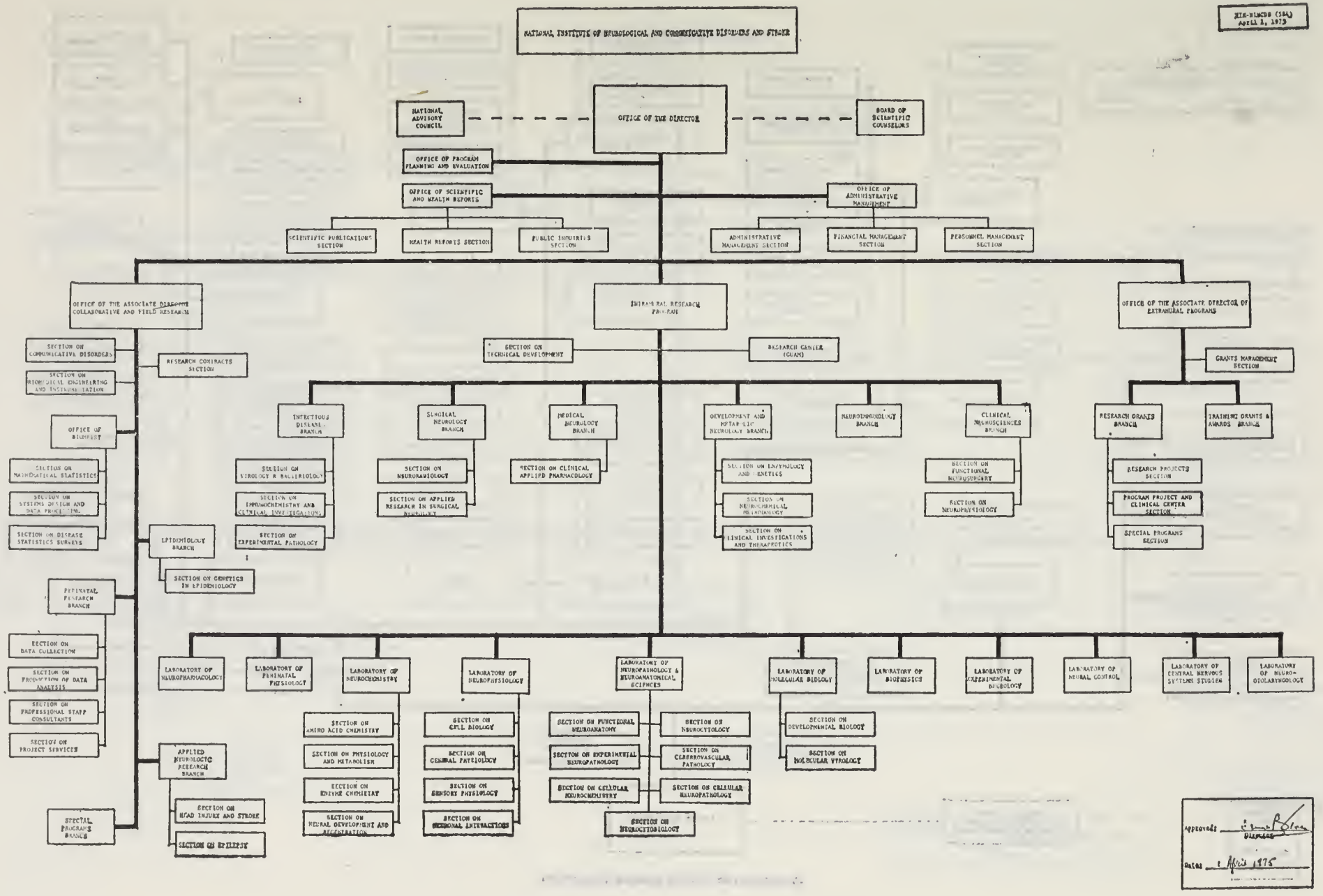
MOLECULAR BIOLOGY SECTION
OLDER VIRAL DISEASES SECTION
ANIMAL MAINTENANCE AND SERVICES SECTION
ZOONOSES SECTION
RICKETTSIAL DISEASES SECTION
MEDICAL ENTOMOLOGY AND ACAROLOGY SECTION
EPIDEMIOLOGY SECTION
LABORATORY OF IMMUNOLOGY
LABORATORY OF CLINICAL INVESTIGATION
ALLERGIC DISEASES SECTION
CLINICAL IMMUNOLOGY SECTION
CLINICAL MYCOLOGY SECTION
BIOLOGIC STRUCTURE SECTION
CLINICAL PHYSIOLOGY SECTION
CLINICAL ALLERGY & HYPERSENSITIVITY SECTION
MEDICAL VIROLOGY SECTION
CLINICAL PARASITOLOGY SECTION
LABORATORY OF BIOLOGY OF VIRUSES
BIOCHEMICAL VIROLOGY SECTION
MACROMOLECULAR BIOLOGY SECTION
PHYSICAL BIOCHEMISTRY SECTION
MOLECULAR BIOACTIVE SECTION
LABORATORY OF PARASITIC DISEASES
PHYSIOLOGY AND BIOCHEMISTRY SECTION
CELL BIOLOGY AND IMMUNOLOGY SECTION
HOST-PARASITE RELATIONS SECTION
PARASITE GROWTH AND DIFFERENTIATION SECTION
PACIFIC RESEARCH SECTION
MALARIA SECTION
PRIMATE MALARIA UNIT
LABORATORY OF VIRAL DISEASES
VIRAL ONCOLOGY SECTION
CELLULAR VIROLOGY SECTION
MOLECULAR VIROLOGY SECTION
LABORATORY OF INFECTIOUS DISEASES
RESPIRATORY VIRUSES SECTION
EPIDEMIOLOGY SECTION
MYCOPLASMA SECTION
HEPATITIS VIRUS SECTION
LABORATORY OF STREPTOCOCCAL DISEASES
LABORATORY OF MICROBIAL IMMUNITY
EXPERIMENTAL PATHOLOGY SECTION
MICROBIOLOGY AND IMMUNOLOGY SECTION
LABORATORY OF MICROBIOLOGY
BACTERIAL STRUCTURE AND FUNCTION SECTION
MEDICAL MYCOLOGY SECTION
IMMUNOLOGY SECTION
RESEARCH RESOURCES BRANCH
TRANSPLANTATION AND IMMUNOLOGY BRANCH
INFECTIOUS DISEASE BRANCH
GEOGRAPHIC MEDICINE BRANCH
U.S. - JAPAN PROGRAM SECTION
ICMR SECTION
REVIEW AND EVALUATION BRANCH
PROGRAM ANALYSIS SECTION
LATA CONTROL SECTION
GRANTS MANAGEMENT & OPERATIONS BRANCH
ALLERGY AND IMMUNOLOGY BRANCH
BACTERIAL AND MYCOTIC DISEASES BRANCH
BIOCHEMISTRY AND PHYSIOLOGY BRANCH
PARASITOLOGY AND MEDICAL ENTOMOLOGY BRANCH
VIRAL DISEASES BRANCH
Approved


NIH-NINCDS (5R4)
April 1, 1975
NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE
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OFFICE OF ADMINISTRATIVE MANAGEMENT
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HEALTH REPORTS SECTION
PUBLIC INQUIRIES SECTION
ADMINISTRATIVE MANAGEMENT SECTION
FINANCIAL MANAGEMENT SECTION
PERSONNEL MANAGEMENT SECTION
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INTRAMURAL RESEARCH PROGRAM
OFFICE OF THE ASSOCIATE DIRECTOR OF EXTRAMURAL PROGRAMS
SECTION ON COMMUNICATIVE DISORDERS
SECTION ON BIOMEDICAL ENGINEERING AND INSTRUMENTATION
RESEARCH CONTRACTS SECTION
SECTION ON TECHNICAL DEVELOPMENT
RESEARCH CENTER (GUAM)
GRANTS MANAGEMENT SECTION
OFFICE OF BIOMETRY
SECTION ON MATHEMATICAL STATISTICS
SECTION ON SYSTEMS DESIGN AND DATA PROCESSING
SECTION ON DISEASE STATISTICS SURVEYS
INFECTIOUS DISEASES BRANCH
SECTION ON VIROLOGY & BACTERIOLOGY
SECTION ON IMMUNOCHEMISTRY AND CLINICAL INVESTIGATIONS
SECTION ON EXPERIMENTAL PATHOLOGY
SURGICAL NEUROLOGY BRANCH
SECTION ON NEURORADIOLOGY
SECTION ON APPLIED RESEARCH IN SURGICAL NEUROLOGY
MEDICAL NEUROLOGY BRANCH
SECTION ON CLINICAL APPLIED PHARMACOLOGY
DEVELOPMENTAL AND METABOLIC NEUROLOGY BRANCH
SECTION ON EMBRYOLOGY AND GENETICS
SECTION ON NEUROCHEMICAL PATHOLOGY
SECTION ON CLINICAL INVESTIGATIONS AND THERAPEUTICS
NEUROIMMUNOLOGY BRANCH
CLINICAL NEUROSCIENCES BRANCH
SECTION ON FUNCTIONAL NEUROSURGERY
SECTION ON NEUROPHYSIOLOGY
RESEARCH GRANTS BRANCH
RESEARCH PROJECTS SECTION
PROGRAM PROJECT AND CLINICAL CENTER SECTION
SPECIAL PROGRAMS SECTION
TRAINING GRANTS & AWARDS BRANCH
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SECTION ON GENETICS IN EPIDEMIOLOGY
PERINATAL RESEARCH BRANCH
SECTION ON DATA COLLECTION
SECTION ON PRODUCTION OF DATA ANALYSIS
SECTION ON PROFESSIONAL STAFF CONSULTANTS
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SPECIAL PROGRAMS BRANCH
APPLIED NEUROLOGIC RESEARCH BRANCH
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SECTION ON EPILEPSY
LABORATORY OF NEUROPHARMACOLOGY
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SECTION ON AMINO ACID CHEMISTRY
SECTION ON PHYSIOLOGY AND METABOLISM
SECTION ON ENZYME CHEMISTRY
SECTION ON NEURAL DEVELOPMENT AND MATURATION
LABORATORY OF NEUROPHYSIOLOGY
SECTION ON CELL BIOLOGY
SECTION ON GENERAL PHYSIOLOGY
SECTION ON SENSORY PHYSIOLOGY
SECTION ON REGIONAL INTERACTIONS
LABORATORY OF NEUROPATHOLOGY & NEUROANATOMICAL SCIENCES
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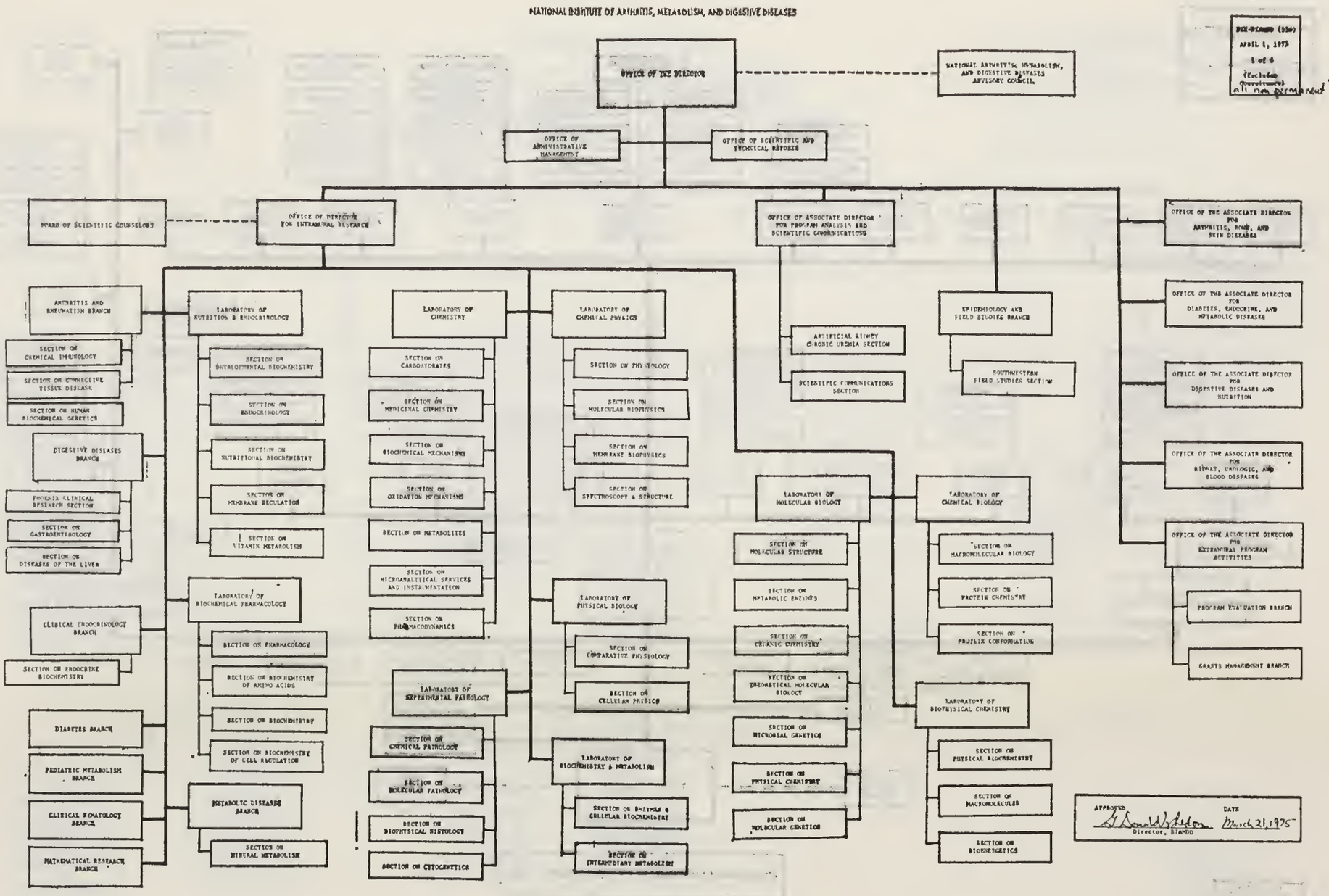
LABORATORY OF NEURO-OTOLARYNGOLOGY
Approved:
DIRECTOR
Date: 1 April 1975


NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES
OFFICE OF THE DIRECTOR
NATIONAL ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES ADVISORY COUNCIL
OFFICE OF ADMINISTRATIVE MANAGEMENT
OFFICE OF SCIENTIFIC AND TECHNICAL REPORTS
BOARD OF SCIENTIFIC COUNSELORS
OFFICE OF DIRECTOR FOR INTRAMURAL RESEARCH
OFFICE OF ASSOCIATE DIRECTOR FOR PROGRAM ANALYSIS AND SCIENTIFIC COORDINATIONS
OFFICE OF THE ASSOCIATE DIRECTOR FOR ARTHRITIS, BONE, AND SKIN DISEASES
OFFICE OF THE ASSOCIATE DIRECTOR FOR DIABETES, ENDOCRINE, AND METABOLIC DISEASES
OFFICE OF THE ASSOCIATE DIRECTOR FOR DIGESTIVE DISEASES AND NUTRITION
OFFICE OF THE ASSOCIATE DIRECTOR FOR RENAL, UROLOGIC, AND BLOOD DISEASES
OFFICE OF THE ASSOCIATE DIRECTOR FOR EXTRAMURAL PROGRAM ACTIVITIES
PROGRAM EVALUATION BRANCH
GRANTS MANAGEMENT BRANCH
ARTHRITIS AND RHEUMATISM BRANCH
SECTION ON CHEMICAL IMMUNOLOGY
SECTION ON CONNECTIVE TISSUE DISEASE
SECTION ON HUMAN BIOCHEMICAL GENETICS
DIGESTIVE DISEASES BRANCH
PHOENIX CLINICAL RESEARCH SECTION
SECTION ON GASTROENTEROLOGY
SECTION ON DISEASES OF THE LIVER
CLINICAL ENDOCRINOLOGY BRANCH
SECTION ON ENDOCRINE BIOCHEMISTRY
DIABETES BRANCH
PEDIATRIC METABOLISM BRANCH
CLINICAL HEMATOLOGY BRANCH
MATHEMATICAL RESEARCH BRANCH
LABORATORY OF NUTRITION & ENDOCRINOLOGY
SECTION ON DEVELOPMENTAL BIOCHEMISTRY
SECTION ON ENDOCRINOLOGY
SECTION ON NUTRITIONAL BIOCHEMISTRY
SECTION ON MEMBRANE REGULATION
SECTION ON VITAMIN METABOLISM
LABORATORY OF BIOCHEMICAL PHARMACOLOGY
SECTION ON PHARMACOLOGY
SECTION ON BIOCHEMISTRY OF AMINO ACIDS
SECTION ON BIOCHEMISTRY
SECTION ON BIOCHEMISTRY OF CELL REGULATION
METABOLIC DISEASES BRANCH
SECTION ON MINERAL METABOLISM
LABORATORY OF CHEMISTRY
SECTION ON CARBOHYDRATES
SECTION ON MEDICINAL CHEMISTRY
SECTION ON BIOCHEMICAL MECHANISMS
SECTION ON OXIDATION MECHANISMS
SECTION ON METABOLITES
SECTION ON MICROANALYTICAL SERVICES AND INSTRUMENTATION
SECTION ON PHARMACODYNAMICS
LABORATORY OF EXPERIMENTAL PATHOLOGY
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SECTION ON ENZYMOLOGY & CELLULAR BIOCHEMISTRY
SECTION ON INTERMEDIARY METABOLISM
ARTIFICIAL KIDNEY CHRONIC UREMIA SECTION
SCIENTIFIC COMMUNICATIONS SECTION
EPIDEMIOLOGY AND FIELD STUDIES BRANCH
SOUTHWESTERN FIELD STUDIES SECTION
LABORATORY OF MOLECULAR BIOLOGY
SECTION ON MOLECULAR STRUCTURE
SECTION ON METABOLIC ENZYMES
SECTION ON ORGANIC CHEMISTRY
SECTION ON IMMUNOLOGICAL MOLECULAR BIOLOGY
SECTION ON MICROBIAL GENETICS
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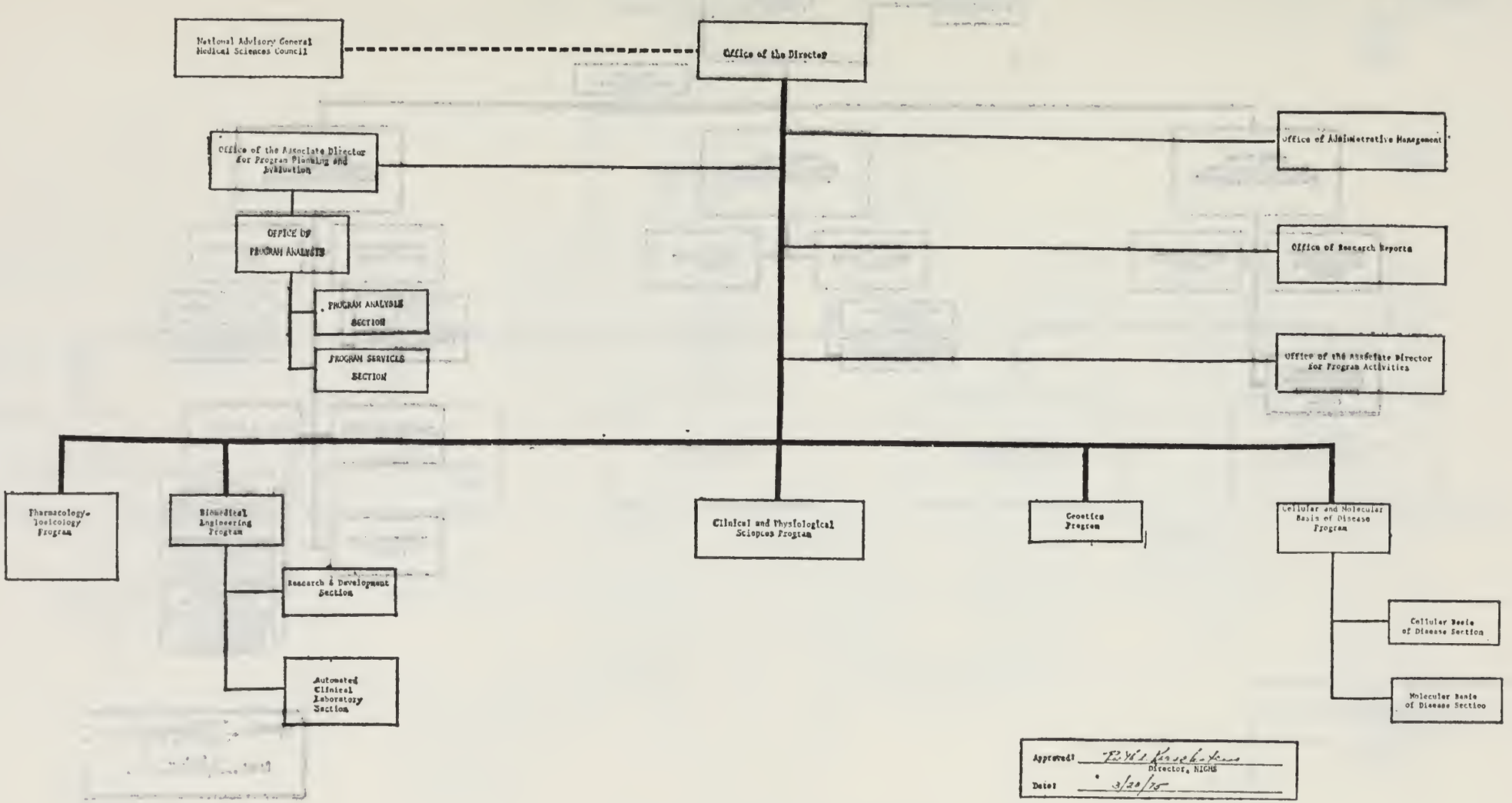
LABORATORY OF CHEMICAL BIOLOGY
SECTION ON MACROMOLECULAR BIOLOGY
SECTION ON PROTEIN CHEMISTRY
SECTION ON PROTEIN CONFORMATION
LABORATORY OF BIOPHYSICAL CHEMISTRY
SECTION ON PHYSICAL BIOCHEMISTRY
SECTION ON MACROMOLECULES
SECTION ON BIOENERGETICS
APPROVED
Director, NIAMDD
DATE
March 21, 1975
APRIL 1, 1975
5 of 6
(Excludes all non permanent)

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

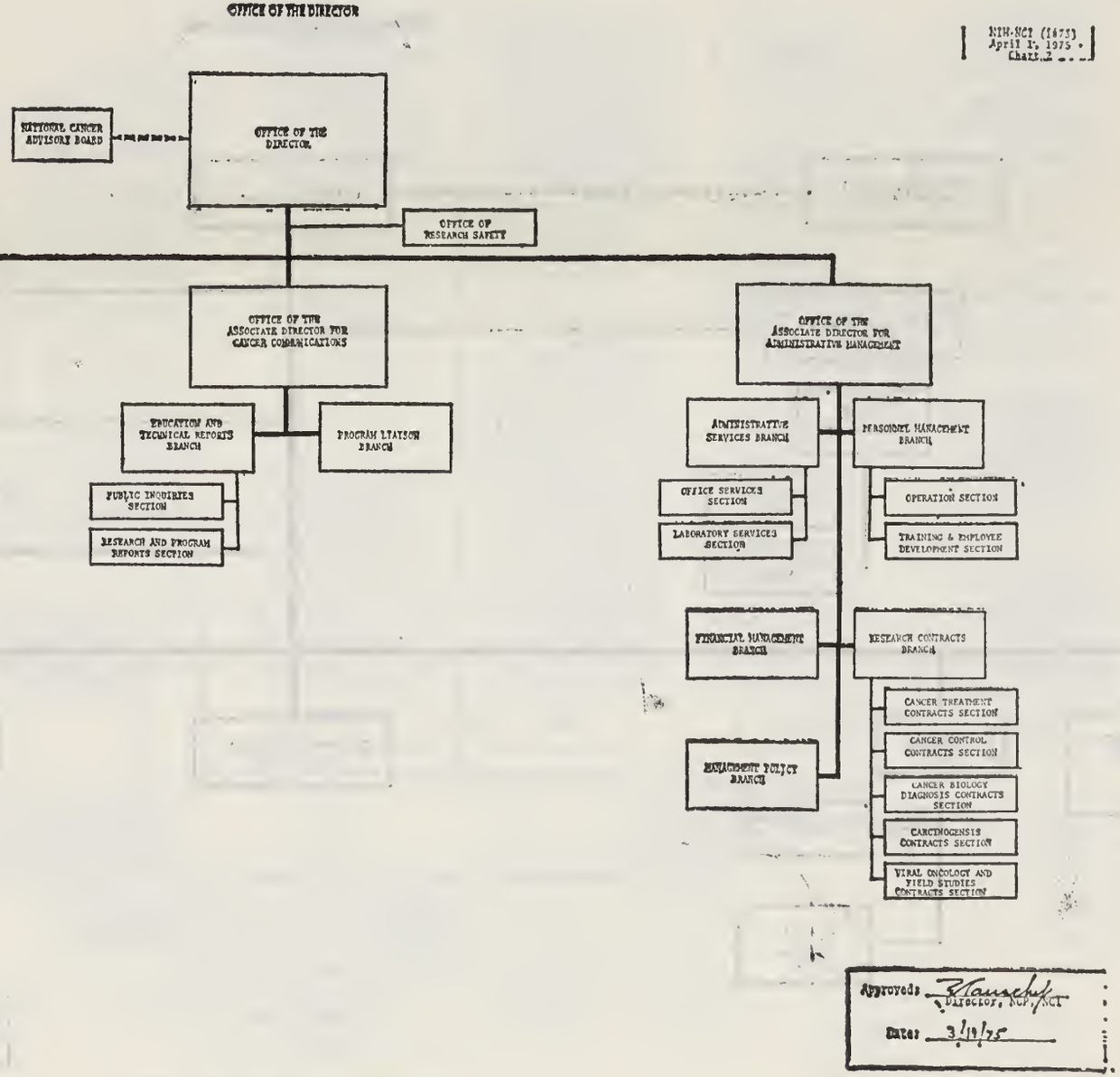
NIH-NIGMS (152)
April 1, 1975
Chart I



Approved: Ruth Kirschstein
Director, NIGMS

Date: 3/20/75

NIH-NCI (1675)
April 1, 1975
Chart 2

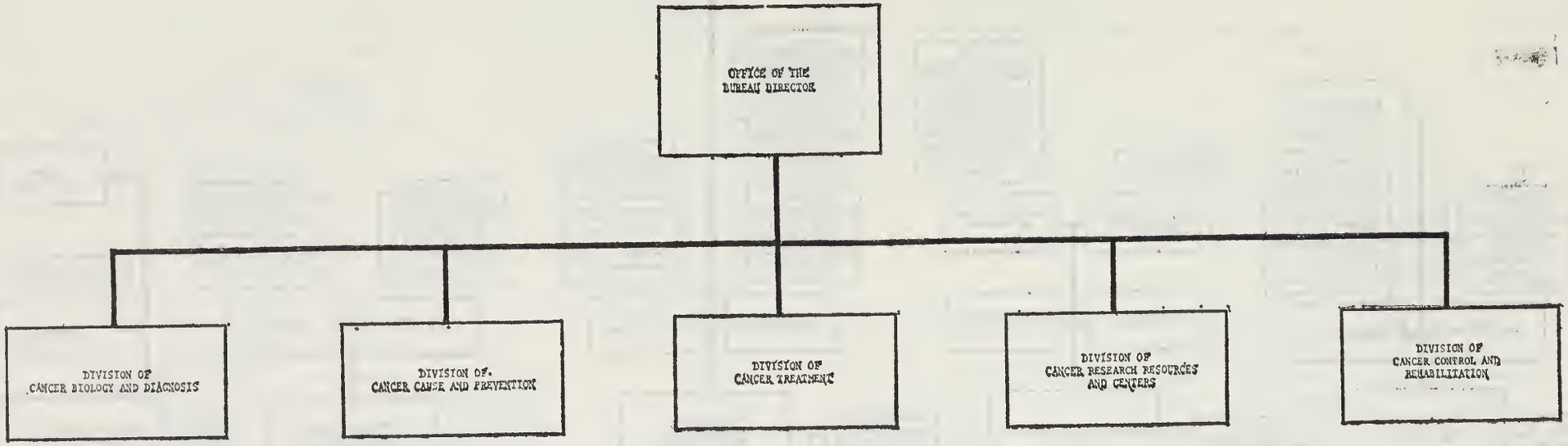


Approved: _____ Director, NCP/NCI

Date: 3/19/75

NIH-NCI (1873)
April 1, 1975
Chart 1

NATIONAL CANCER INSTITUTE

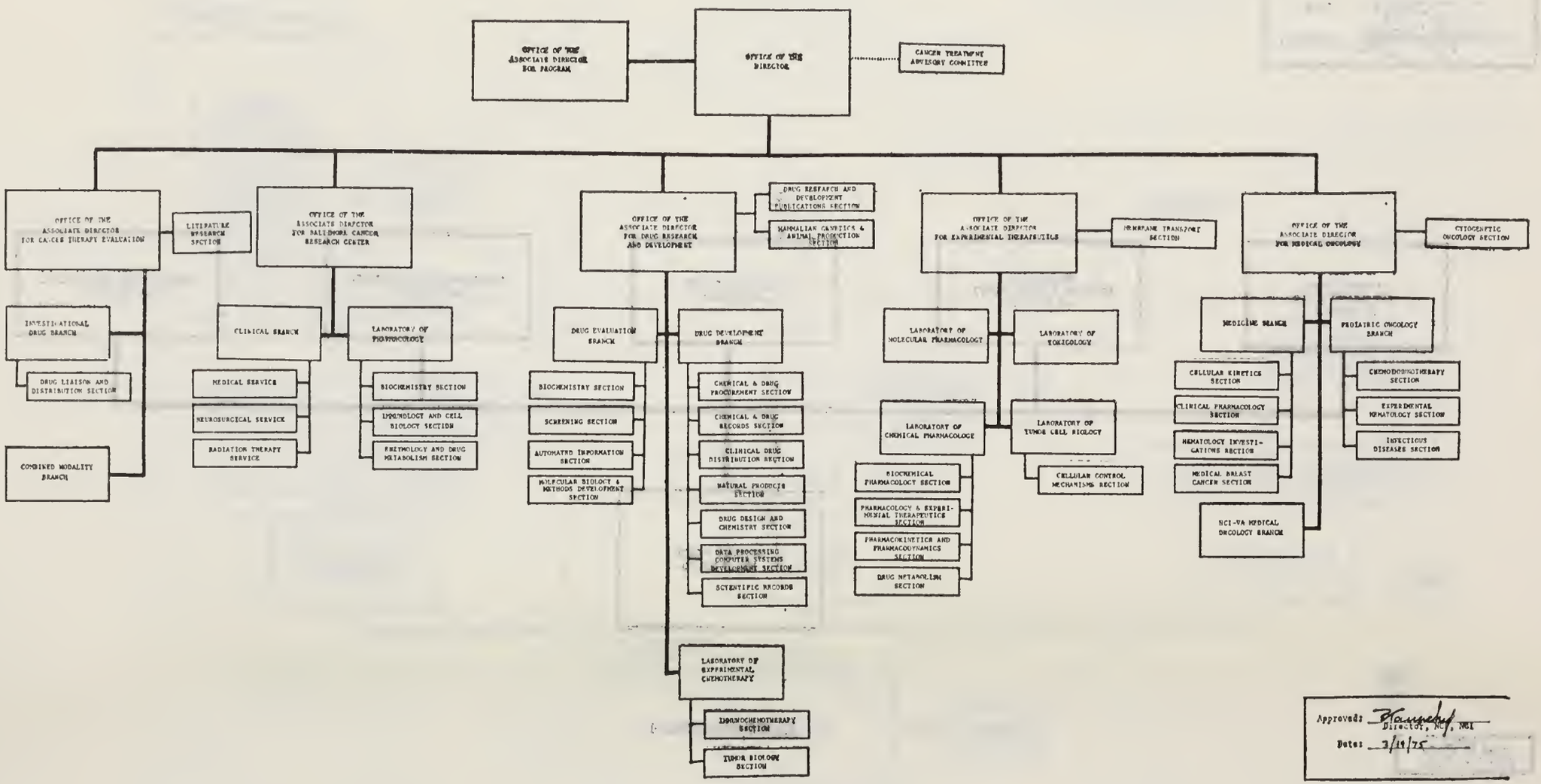


Approved: _____
Director, NCI, NCI

Date: 3/19/75

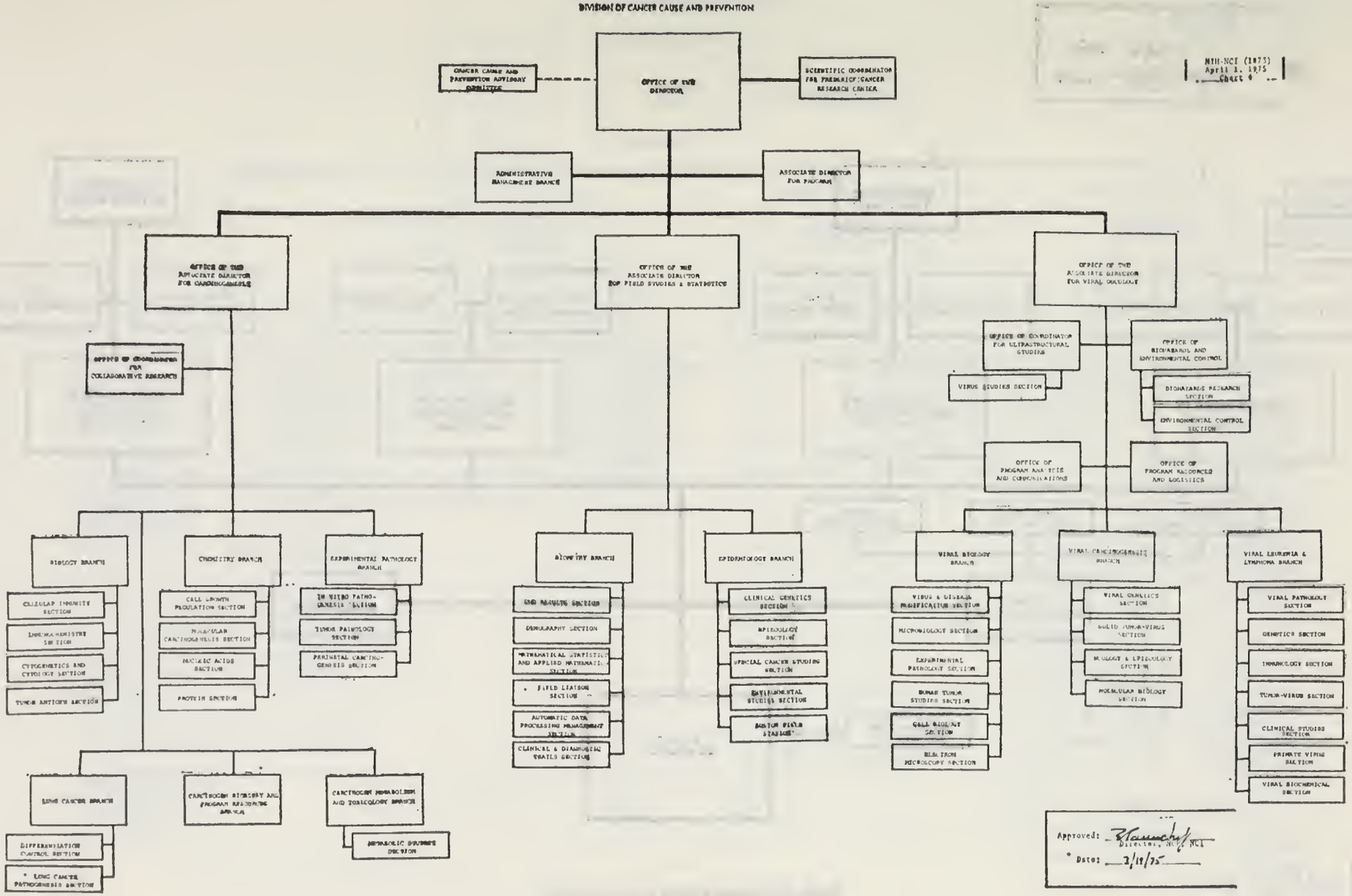
DIVISION OF CANCER TREATMENT

NIH-NCI (1973)
April 1, 1975
Chart 3



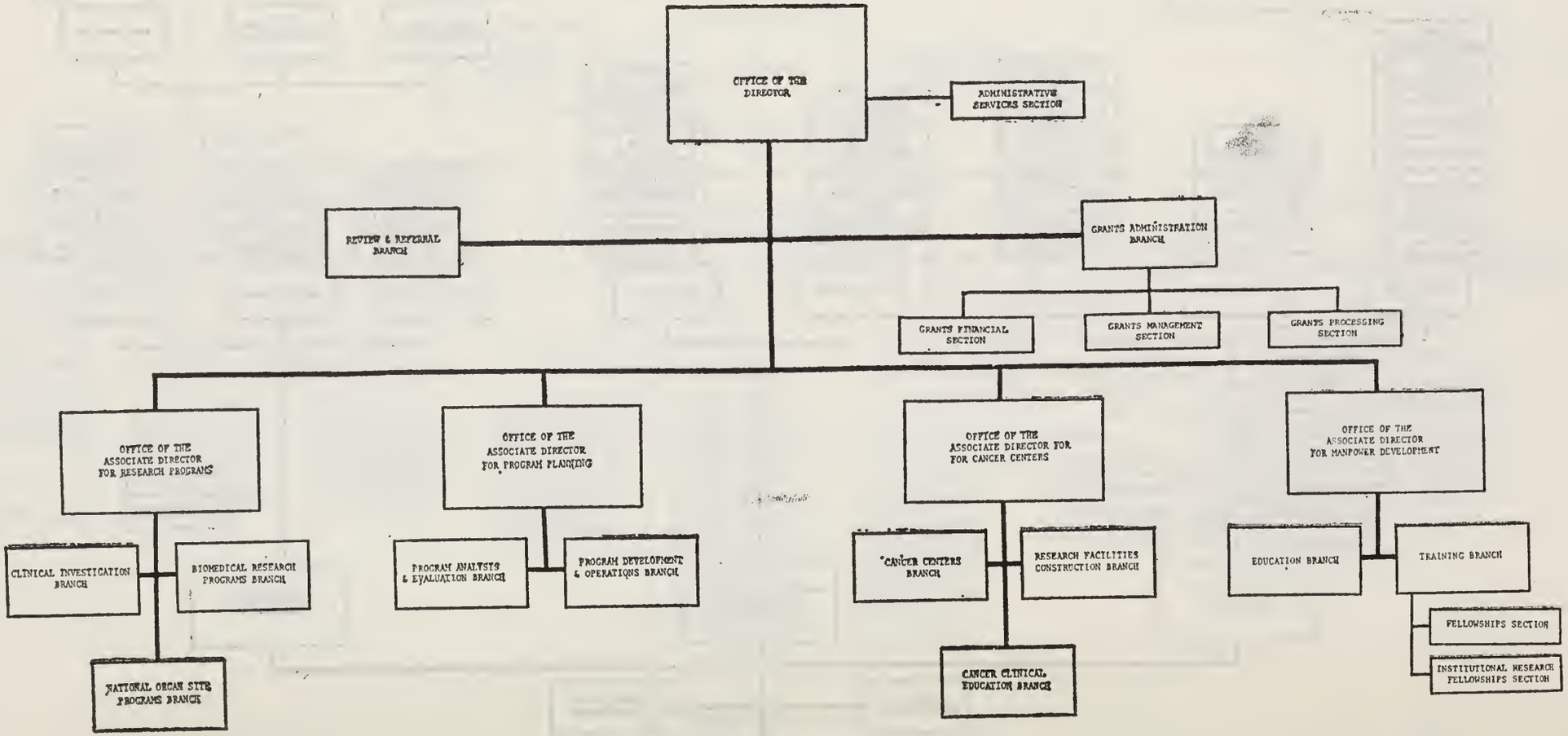
Approved: _____
Director, NCI, NCI

Date: 3/19/75


DIVISION OF CANCER CAUSE AND PREVENTION
CANCER CAUSE AND PREVENTION ADVISORY COMMITTEE
OFFICE OF THE DIRECTOR
SCIENTIFIC COORDINATOR FOR FREDERICK CANCER RESEARCH CENTER
NIH-NCI (1975) April 1, 1975 Chart 4
ADMINISTRATIVE MANAGEMENT BRANCH
ASSOCIATE DIRECTOR FOR PROGRAM
OFFICE OF THE ASSOCIATE DIRECTOR FOR CARCINOGENESIS
OFFICE OF THE ASSOCIATE DIRECTOR FOR FIELD STUDIES & STATISTICS
OFFICE OF THE ASSOCIATE DIRECTOR FOR VIRAL ONCOLOGY
OFFICE OF COORDINATOR FOR COLLABORATIVE RESEARCH
OFFICE OF COORDINATOR FOR ULTRASTRUCTURAL STUDIES
VIRUS STUDIES SECTION
OFFICE OF BIOHAZARD AND ENVIRONMENTAL CONTROL
BIOHAZARDS RESEARCH SECTION
ENVIRONMENTAL CONTROL SECTION
OFFICE OF PROGRAM ANALYSIS AND COMMUNICATIONS
OFFICE OF PROGRAM RESOURCES AND LOGISTICS
BIOLOGY BRANCH
CELLULAR IMMUNITY SECTION
IMMUNOCHEMISTRY SECTION
CYTOGENETICS AND CYTOLOGY SECTION
TUMOR ANTIGENS SECTION
CHEMISTRY BRANCH
CELL GROWTH REGULATION SECTION
MOLECULAR CARCINOGENESIS SECTION
NUCLEIC ACIDS SECTION
PROTEIN SECTION
EXPERIMENTAL PATHOLOGY BRANCH
IN VITRO PATHOGENESIS SECTION
TUMOR PATHOLOGY SECTION
PERINATAL CARCINOGENESIS SECTION
BIOMETRY BRANCH
END RESULTS SECTION
DEMOGRAPHY SECTION
MATHEMATICAL STATISTICS AND APPLIED MATHEMATICS SECTION
FIELD LIAISON SECTION
AUTOMATIC DATA PROCESSING MANAGEMENT SECTION
CLINICAL & DIAGNOSTIC TRAILS SECTION
EPIDEMIOLOGY BRANCH
CLINICAL GENETICS SECTION
EPIDEMIOLOGY SECTION
SPECIAL CANCER STUDIES SECTION
ENVIRONMENTAL STUDIES SECTION
FIELD STATIONS
VIRAL BIOLOGY BRANCH
VIRUS & CELLULAR PROLIFERATION SECTION
MICROBIOLOGY SECTION
EXPERIMENTAL PATHOLOGY SECTION
HUMAN TUMOR STUDIES SECTION
CELL BIOLOGY SECTION
RNA TUMOR VIRUS SECTION
VIRAL CARCINOGENESIS BRANCH
VIRAL GENETICS SECTION
SOLID TUMOR-VIRUS SECTION
MOLOGY & EPIDEMIOLOGY SECTION
MOLECULAR BIOLOGY SECTION
VIRAL LEUKEMIA & LYMPHOMA BRANCH
VIRAL PATHOLOGY SECTION
GENETICS SECTION
IMMUNOLOGY SECTION
TUMOR-VIRUS SECTION
CLINICAL STUDIES SECTION
PRIMATE VIRUS SECTION
VIRAL BIOCHEMICAL SECTION
LUNG CANCER BRANCH
DIFFERENTIATION CONTROL SECTION
LUNG CANCER PATHOGENESIS SECTION
CARCINOGEN THERAPY AND PROGRAM RESOURCES BRANCH
CARCINOGEN METABOLISM AND TOXICOLOGY BRANCH
METABOLIC STUDIES SECTION
Approved:
Director, NCI & NCL
Date: 2/19/75

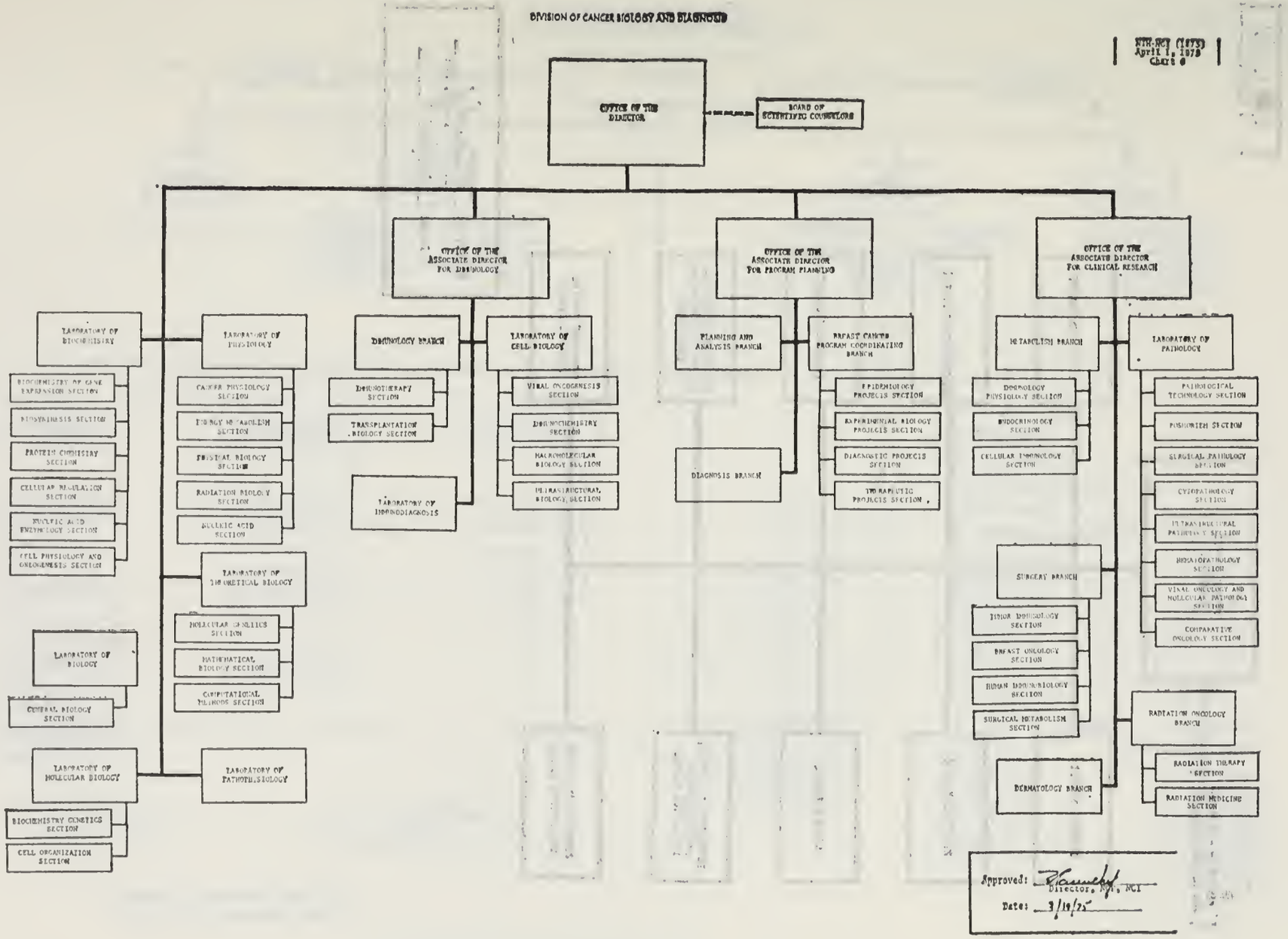
DIVISION OF CANCER RESEARCH RESOURCES AND CENTERS

NIH-NCI (1873)
April 1, 1975
Chart 5



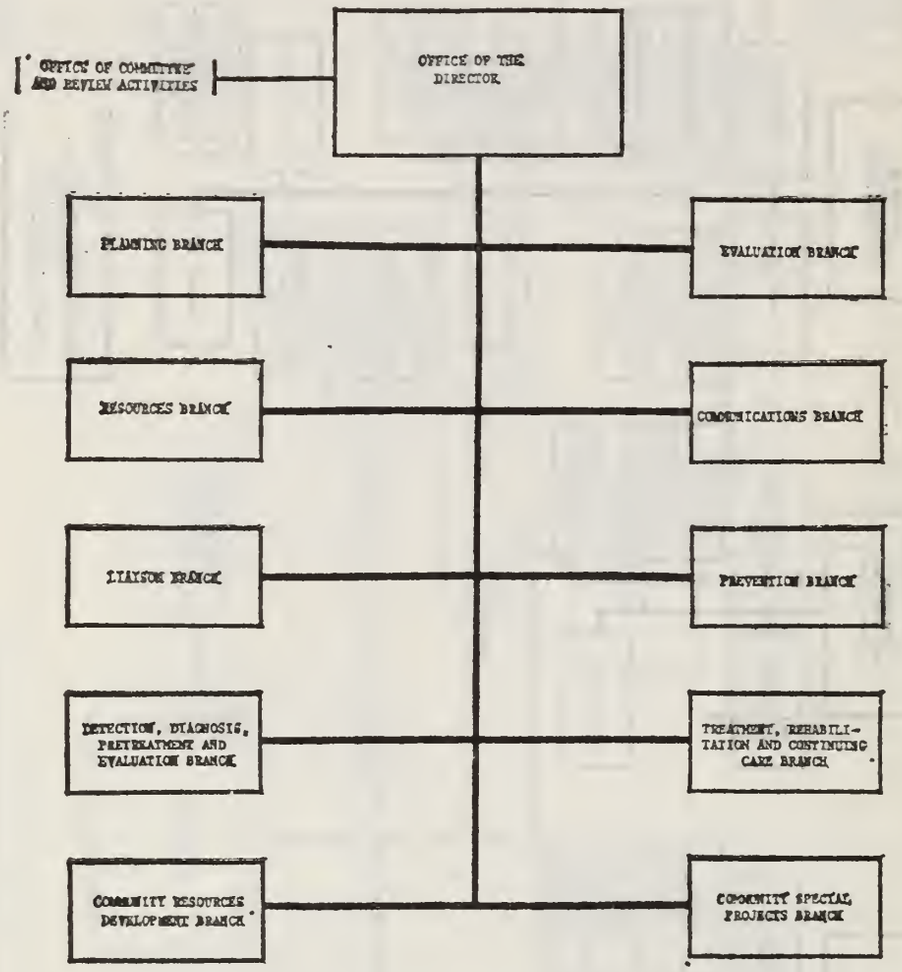
Approved: _____
Director, NCI, NCI

Date: 2/11/75


DIVISION OF CANCER BIOLOGY AND DIAGNOSIS
NIH-NCI (1973)
April 1, 1973
Chart
OFFICE OF THE DIRECTOR
BOARD OF SCIENTIFIC COUNSELORS
OFFICE OF THE ASSOCIATE DIRECTOR FOR IMMUNOLOGY
OFFICE OF THE ASSOCIATE DIRECTOR FOR PROGRAM PLANNING
OFFICE OF THE ASSOCIATE DIRECTOR FOR CLINICAL RESEARCH
LABORATORY OF BIOCHEMISTRY
BIOCHEMISTRY OF GENE EXPRESSION SECTION
BIOSYNTHESIS SECTION
PROTEIN CHEMISTRY SECTION
CELLULAR REGULATION SECTION
NUCLEIC ACID ENZYMOLOGY SECTION
CELL PHYSIOLOGY AND ONCOGENESIS SECTION
LABORATORY OF PHYSIOLOGY
CANCER PHYSIOLOGY SECTION
ENERGY METABOLISM SECTION
BIOPHYSICAL BIOLOGY SECTION
RADIATION BIOLOGY SECTION
NUCLEIC ACID SECTION
LABORATORY OF THEORETICAL BIOLOGY
MOLECULAR GENETICS SECTION
MATHEMATICAL BIOLOGY SECTION
COMPUTATIONAL METHODS SECTION
LABORATORY OF BIOLOGY
GENERAL BIOLOGY SECTION
LABORATORY OF MOLECULAR BIOLOGY
BIOCHEMISTRY GENETICS SECTION
CELL ORGANIZATION SECTION
LABORATORY OF PATHOPHYSIOLOGY
IMMUNOLOGY BRANCH
IMMUNOTHERAPY SECTION
TRANSPLANTATION BIOLOGY SECTION
LABORATORY OF IMMUNODIAGNOSIS
LABORATORY OF CELL BIOLOGY
VIRAL ONCOGENESIS SECTION
IMMUNOCHEMISTRY SECTION
MACROMOLECULAR BIOLOGY SECTION
ULTRASTRUCTURAL BIOLOGY SECTION
PLANNING AND ANALYSIS BRANCH
DIAGNOSIS BRANCH
BREAST CANCER PROGRAM COORDINATING BRANCH
EPIDEMIOLOGY PROJECTS SECTION
EXPERIMENTAL BIOLOGY PROJECTS SECTION
DIAGNOSTIC PROJECTS SECTION
THERAPEUTIC PROJECTS SECTION
METABOLISM BRANCH
ENDOCRINOLOGY PHYSIOLOGY SECTION
ENDOCRINOLOGY SECTION
CELLULAR IMMUNOLOGY SECTION
LABORATORY OF PATHOLOGY
PATHOLOGICAL TECHNOLOGY SECTION
PUBLISHING SECTION
SURGICAL PATHOLOGY SECTION
CYTOPATHOLOGY SECTION
ULTRASTRUCTURAL PATHOLOGY SECTION
HISTOPATHOLOGY SECTION
VIRAL ONCOLOGY AND MOLECULAR PATHOLOGY SECTION
COMPARATIVE ONCOLOGY SECTION
SURGERY BRANCH
JUNIOR IMMUNOLOGY SECTION
BREAST ONCOLOGY SECTION
HUMAN IMMUNOBIOLOGY SECTION
SURGICAL METABOLISM SECTION
DERMATOLOGY BRANCH
RADIATION ONCOLOGY BRANCH
RADIATION THERAPY SECTION
RADIATION MEDICINE SECTION
Approved:
Director, NCI
Date: 3/19/73

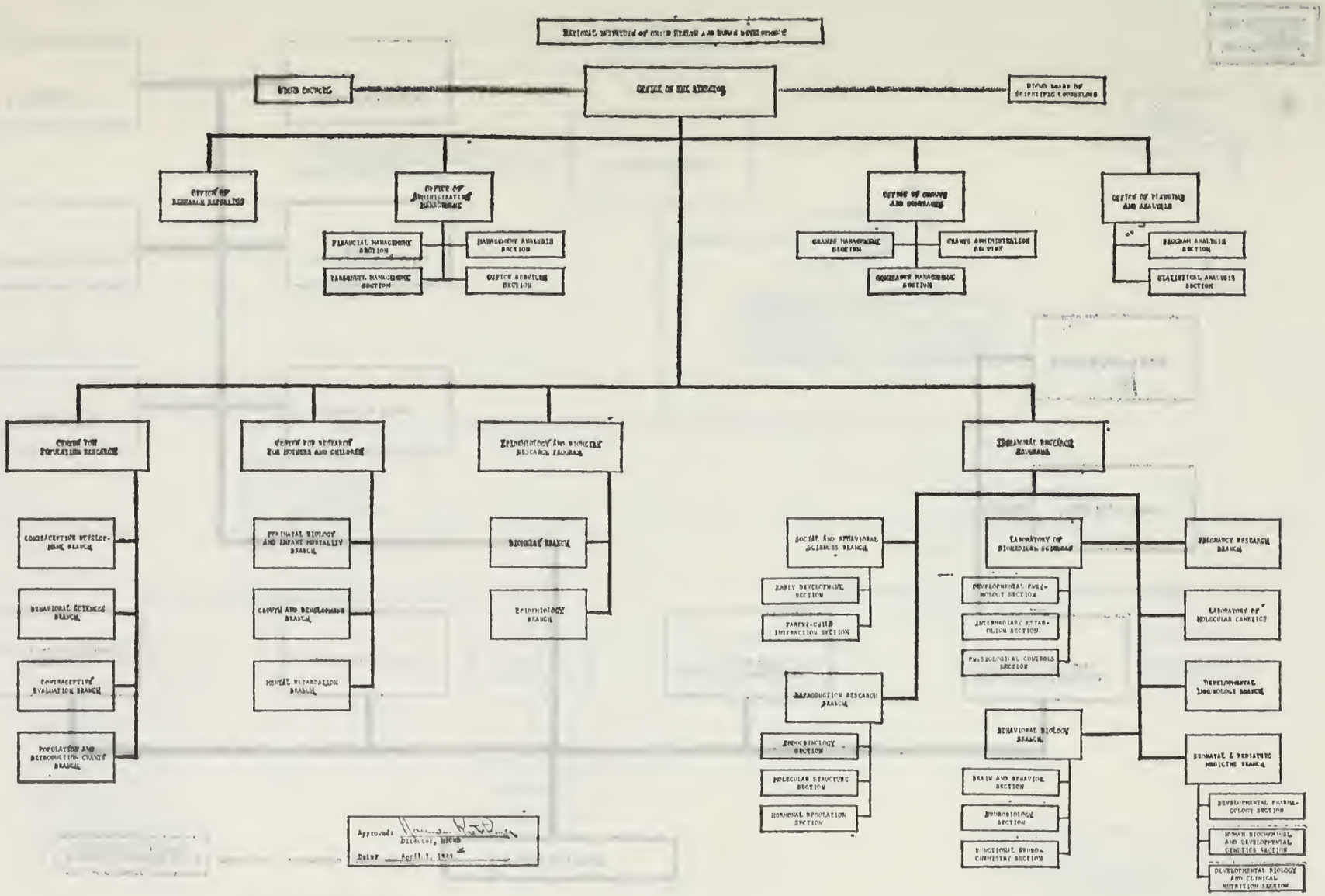
DIVISION OF CANCER CONTROL AND REHABILITATION

NIH-NCI (1873)
April 1, 1975
Chart 7

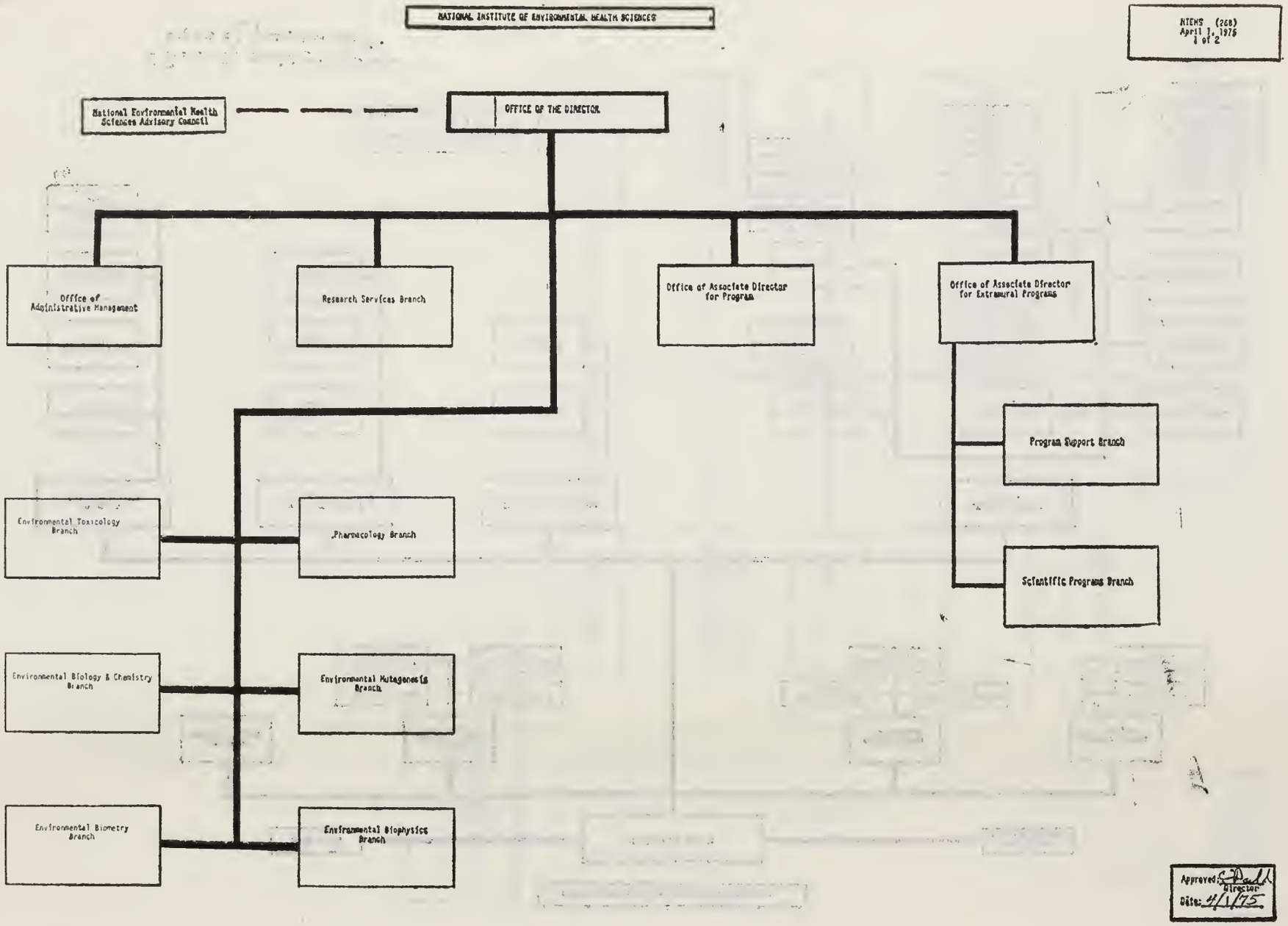


Approved: _____
Director, NCI

Date: 3/19/75

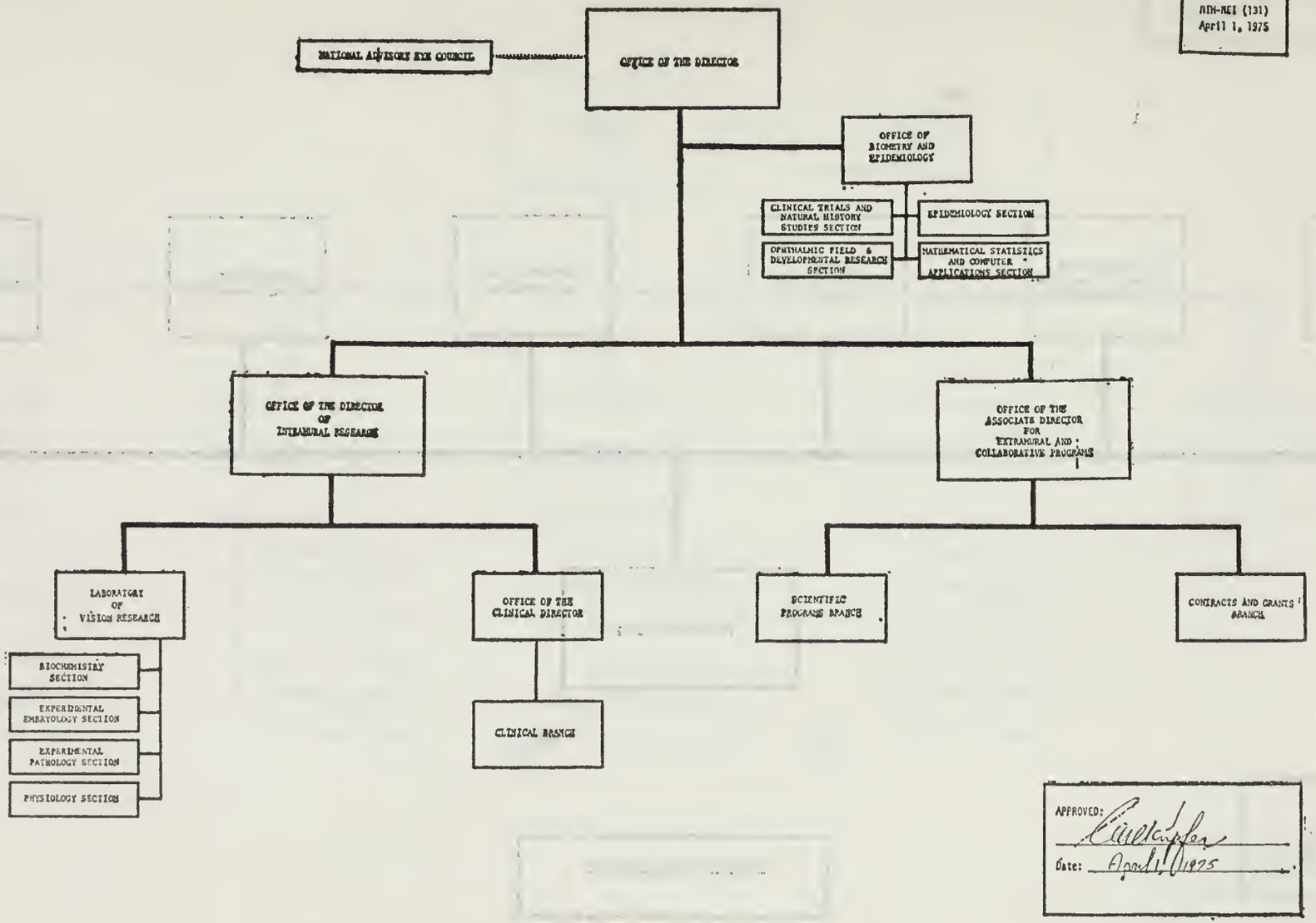


* Proposed; pending approval and establishment of program branch.


NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
NIEHS (268)
April 1, 1976
1 of 2
National Environmental Health Sciences Advisory Council
OFFICE OF THE DIRECTOR
Office of Administrative Management
Research Services Branch
Office of Associate Director for Program
Office of Associate Director for Extramural Programs
Program Support Branch
Scientific Programs Branch
Environmental Toxicology Branch
Pharmacology Branch
Environmental Biology & Chemistry Branch
Environmental Mutagenesis Branch
Environmental Biometry Branch
Environmental Biophysics Branch
Approved: Director
Date: 4/1/75

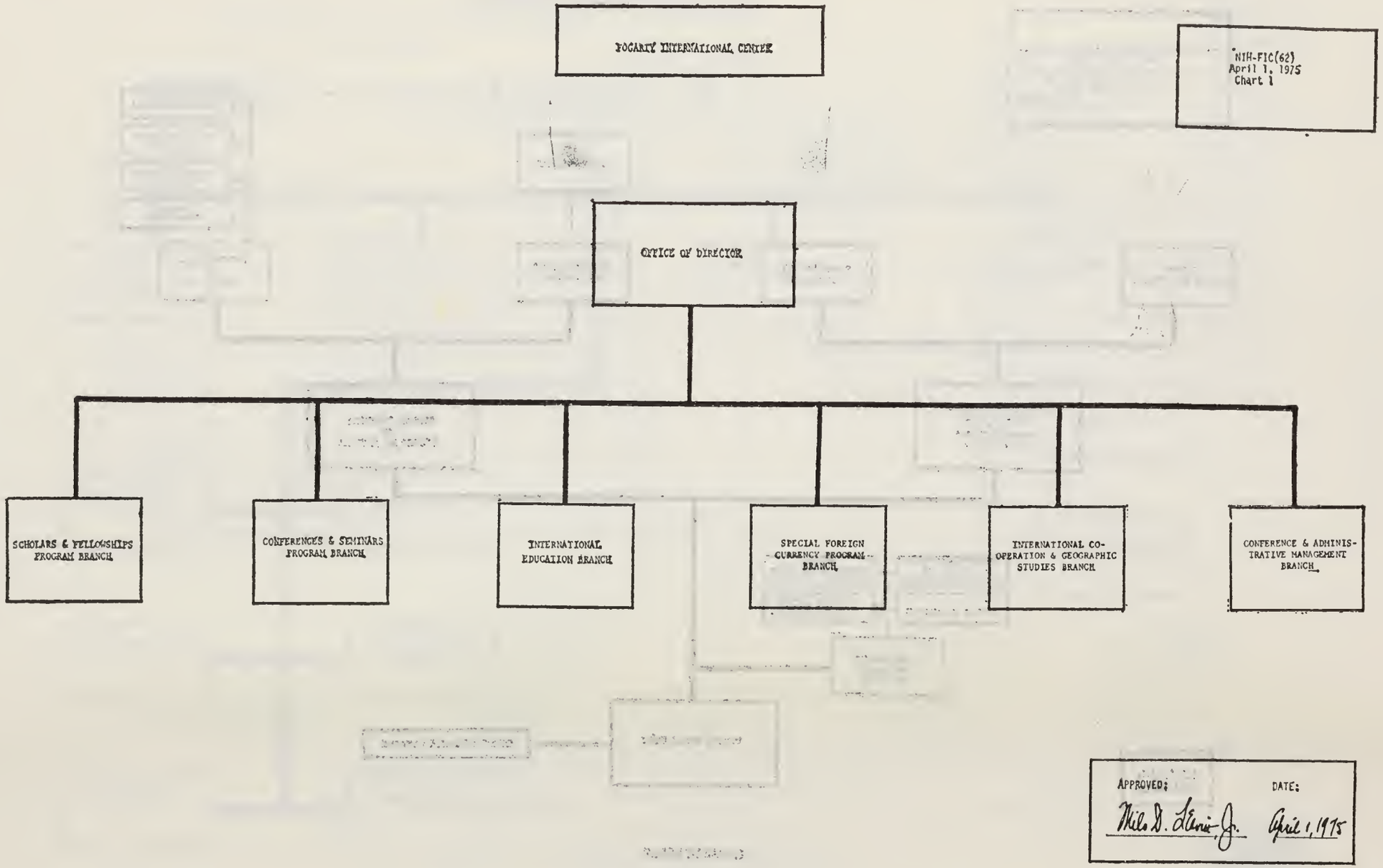
NATIONAL EYE INSTITUTE

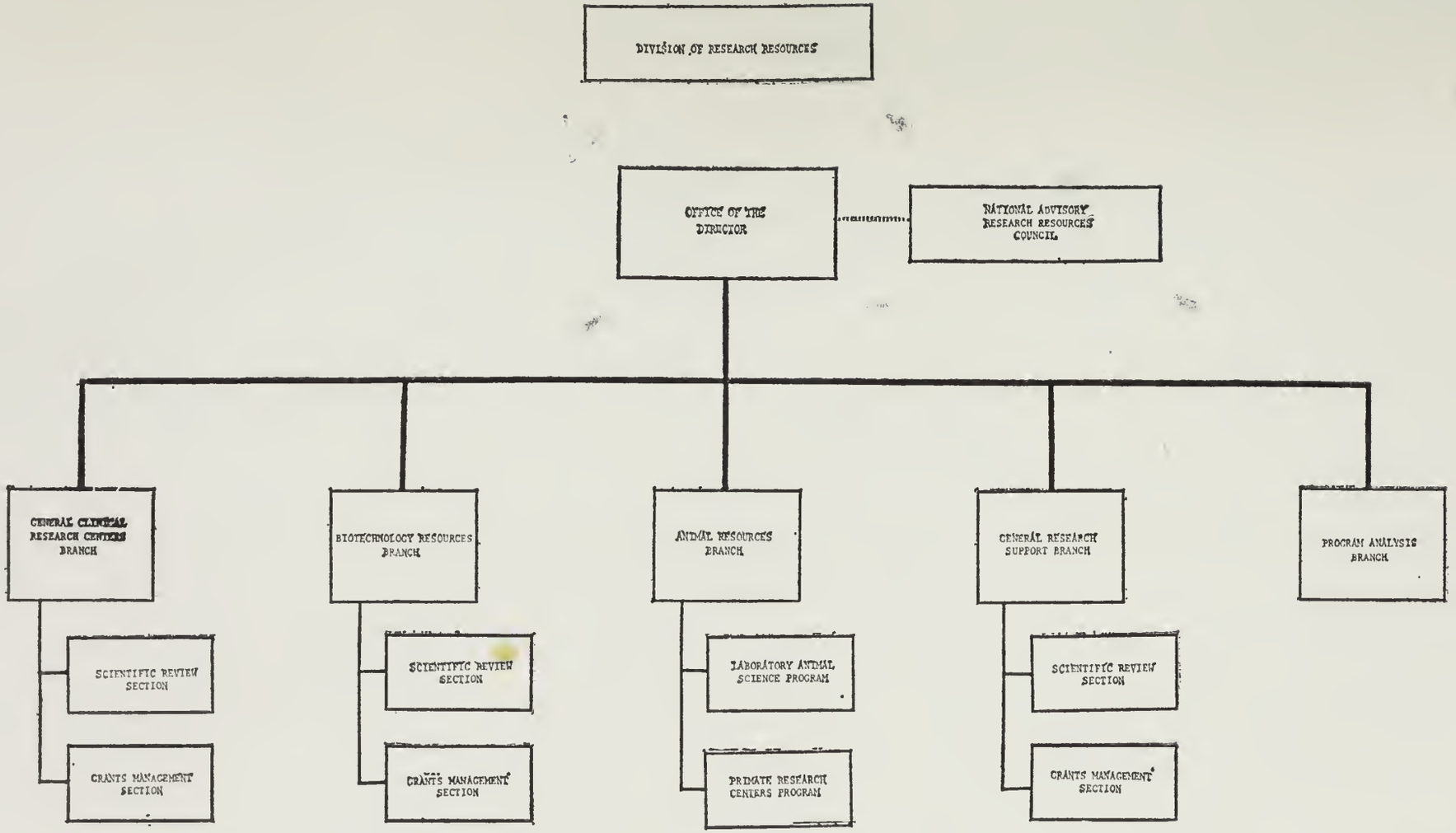
NIH-NEI (131)
April 1, 1975



APPROVED: Carl Taylor

Date: April 1, 1975


FOGARTY INTERNATIONAL CENTER
NIH-FIC(62)
April 1, 1975
Chart 1
OFFICE OF DIRECTOR
SCHOLARS & FELLOWSHIPS PROGRAM BRANCH
CONFERENCES & SEMINARS PROGRAM BRANCH
INTERNATIONAL EDUCATION BRANCH
SPECIAL FOREIGN CURRENCY PROGRAM BRANCH
INTERNATIONAL CO-OPERATION & GEOGRAPHIC STUDIES BRANCH
CONFERENCE & ADMINISTRATIVE MANAGEMENT BRANCH
APPROVED:
Miles D. Devine, Jr.
DATE:
April 1, 1975



Approved: Thomas D Bowery
Director
Date: 3/20/75